Mild Traumatic Brain Injury: Bio-Mechanistic consequences, evaluation, treatment and perspectives of TBI in athletics

By

Andrew Gee

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Dr. Haesun Kim

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Abstract

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Andrew Gee

Dissertation Director

Dr. Haesun Kim

Abstract:

Traumatic Brain Injury particularly of mild severity (mTBI) is a common yet poorly understood phenomenon on the molecular level. Connections between mTBI and chronic neuropathologies have been established, but the molecular and cellular changes caused by mild and/or repeated TBIs remain poorly characterized in their occurrence and significance. The core of this thesis will focus on describing the current state of mTBI research, with a focus on its significance in the field of athletics. Molecular mechanisms following a Traumatic Brain Injury occur in both the acute phase and chronically, in the form of primary injuries including hemorrhage and edema resulting from the impact producing the TBI, and secondary injury consisting of progressive demyelination and neuronal loss due to persistent inflammatory states and cellular microenvironments.

Current understanding of how and why recovery from single, or more commonly, multiple mTBIs may transition into a progressive disease state is poorly understood, with genetic and environmental factors almost certainly playing roles. Current diagnostic
methods post-mTBI consist of subjective neurological evaluations which, while often correctly diagnose injury, lack the ability to provide insight into the biochemical changes occurring in the brain. Computed Tomography and Magnetic Resonance based imaging strategies provide more substantive structural information of the brain but their usage is limited in mTBI cases due to reasons including but not limited to cost, necessity and availability.

The significance of mTBIs outside the sphere of science has historically been very limited and only in the past few decades has a push been made for greater translation of TBI related cause and effect to the general population. Specifically, athletes, a majority of which are adolescents and young adults, are especially at risk due to the nature of sport itself, as well as the culture surrounding high level competition. Greater understanding of the molecular changes underpinning the pathophysiology of mTBI could lead to treatments shortening the recovery time post injury and reducing risk of chronic progressive neurological dysfunction.
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1. Introduction

The human brain, a marvel of evolution catapulting Homo sapiens into the upper echelon of dominance on the global stage. Combining the capacity for complex memory recall, fine motor control, pattern recognition, and predictive capabilities has facilitated the development of tools such as language, science and art, as well as abstractions such as the human consciousness. Undoubtedly, an argument for the brain being the single most important human organ can be substantiated. For all of the importance and power held by the brain, we as humans have still yet to develop many meaningful repair techniques for the nervous system, one of our most critical body systems, and even fewer methods of replicating its functions independently of the organ (think dialysis filtering blood etc). This current lack of understanding is punctuated by an ironic vulnerability of the brain to damage. Admittedly, an argument for the brain being the most relatively well protected organ can be made, but the fragility of an organ protected by a casing of fused bones being responsible for the difference between a homeostatic, self-aware individual and a series of tissues unable to function without direction is slightly paradoxical.

The goal of this review is to examine Traumatic Brain injury, particularly repetitive and/or mild TBI as commonly seen in athletes, and its effects on white matter integrity and cognitive deficits. Acute pathology of TBI is relatively well characterized in moderate-severe forms of TBI whereas longer term effects have more recently been brought into the limelight as connections between mild traumatic brain injury/subconcussive impact and long term deficits have been made and disseminated into the public sphere in the context of contact sports and its connection to chronic traumatic encephalopathy (CTE). Although cause-
effect has been established, functional knowledge of recovery mechanisms post-TBI has still not been effectively translated into clinical practice or therapeutic treatments. Filling gaps in current understanding of injury on a cellular level and the propensity in developing long term cognitive deficits, particularly in repetitive mTBI scenarios, could lead to development of treatment options available to individuals sustaining injuries anywhere from sports to battlefield injuries.

TBI has always been a topic of conversation in the athletics community due to the frequency it is encountered. Being a collegiate athlete myself, I can personally attest to the cultural viewpoints held by athletes towards concussions, specifically as frustrating injuries with few outward signs that inhibit participation in a competitive scene. I’ve watched teammates go above and beyond in their deceptions towards athletic training staff whose goal is only to help and protect them, just so they can continue practicing or play in the upcoming game. Advancements in technology and awareness surrounding the issue of concussions in sports have gained traction in the past decade, but can I confidently say the issue is well addressed in the environment? No, I cannot.

2. **Background**

Traumatic brain injury (TBI) occurs when mechanical energy is directly transferred to the head through an impact such as blunt or piercing trauma causing the brain to strike the inner skull or breach the skull cavity and damage tissue directly, or indirectly in cases involving inertia exerting compressive or shear forces on brain tissues (McAllister 2). TBI pathology can be divided into two temporal stages, primary consisting of damage sustained in the acute stage post-injury, and secondary, chronic damage potentially resulting in long term consequences.
2.1 Biomechanics of TBI - Primary injury

The American College of Surgeons defines a primary TBI as the brain damage occurring at the time of impact and which is refractory to most treatments (Douglas 2019). This definition includes penetrating injuries which involve direct interaction of a foreign object and the brain which damages structures, as well as closed head injuries resulting from contact or inertial forces causing internal loading resulting in linear, rotational, and shear forces on brain tissue (Meaney 2011).

Contact forces are more easily understood as the force of impact when the head is struck or strikes a surface. The associated forces cause the brain to impact the skull, resulting in damage and disruption if the force experienced is greater than the meninges capacity to cushion the blow and distribute the impact (Hemphill 2015). Inertial forces are more obscure, as the damaging forces involved are transferred to the brain without contact with an object or surface. For example, shear forces generated by rapid head rotation are generally understood as one of the primary mechanisms of injury in concussion. The highly organized and heterogeneous nature of the complex brain makes these tissues very susceptible to this type of injury pathology, cytoskeletal components spanning long regions of axons being particularly vulnerable due to their physical properties (Meaney 2011).

Pathologies including edema, contusion and hemorrhage making up larger lesion types, combined with microscale damage including diffuse axonal injury (DAI) and vascular damage, comprise the injury types due to the primary mechanical damage. (Hemphill 2015). Whereas peripheral nerves readily regenerate, recovery of damaged axons is
negligible in the CNS, often leading to permanent loss of neurons and associated myelin following DAI.

Myelination maintained by oligodendrocytes plays a critical role in saltatory conduction of action potentials down axons in the CNS as function of these myelinated sections is to insulate and accelerate the electrical action potential travelling down the axon by restricting ion exchange to the small exposed sections containing high densities of ion transporters. Myelin integrity and oligodendrocyte survival have also been observed as key factors in short term and long term TBI pathologies, as well as neurodegenerative diseases. The vulnerability of myelinated axons cannot be understated, “Of these circuit components, long axons traversing the white matter are particularly susceptible to the compression, torsion, and tension forces that cause axonal cytoskeleton breakdown followed by secondary neurodegeneration within WM tracts” (Marion 2018).

2.2 Biomechanics of TBI - Secondary injury

After the initial trauma of a TBI, disruption of cellular and molecular processes and structures combined with inflammatory response contributes to secondary damage. Transduction of force to the brain may result in “mechanoporation”, the disruption of the plasma membrane through physical stretching in one of two dimensions, causing a cascade beginning with Na+/K+ imbalance followed by voltage-gated Ca2+ channel activation increasing intracellular calcium levels resulting in release of neurotransmitters including glutamate. Activation of presynaptic neurons in this way causes a glutamate release and calcium influx in postsynaptic neurons, triggering a feedback loop (Barkhoudarian 2011). Intracellular Ca2+ release resulting in activation of apoptotic pathways, production of free radicals and increased metabolic demand contribute to the
persistent metabolic and cellular dysfunction seen in varying severities of TBI (Galgano 2017). Activation of microglial cells due to ionic imbalance leading to a persistent neuroinflammatory state has also been implicated as a factor in long term outcome and recovery and may correlate with injury severity (Shultz 2017).

TBI varies from a transient insult in its mild forms, to a disabling injury in its more severe cases. Symptoms of TBI range from transient cognitive deficits, speech and language impairment, and mood perturbations in mild traumatic brain injury (mTBI), also referred to interchangeably as concussions in common usage, to permanent motor function loss, vegetative/comatose states, and death in severe traumatic brain injury (CDC 2015)(NIH 2020). While short term outcomes in varying severities of TBI are relatively well characterized in literature and awareness programs, information regarding long term dysfunction is poorly described and disseminated to vulnerable populations such as athletes (many of which are adolescents/young adults) who may experience symptoms such as sleep pattern disruption, short term memory recall, and emotional disturbances. These symptoms at such an important developmental stage likely have significant impact on academic and athletic performance, cognitive development, and social integration (Semple 2015).

Recently, increasing interest in long term outcomes of repetitive mild TBIs particularly in athletes has spurred investigation into the correlation between such insults and age related neurodegenerative disease including Chronic Traumatic Encephalopathy (CTE) and Alzheimer's Disease (AD). Evidence suggesting progressive white and gray matter atrophy post-TBI and rmTBI has been shown in multiple studies using immunocytochemical, and imaging techniques, but the complex mechanisms underlying
such changes remain unclear due to confounding genetic and environmental factors (Bramlett 2015). Additionally, observations into long term deficits caused by rmTBI have mainly been studied in adults and relatively little data is available for immature brain experimental models (Fidan 2016).

2.3 Epidemiology

By Centers for Disease Control and Prevention (CDC) estimates, incidence of TBI related emergency department (ED) visits in the United States approximated 2.5 million in 2010, with young children 0-4, adolescents 15-19, and seniors 75 years and older being the most represented groups in the total incident population (Table 1). The numbers approximated are almost certainly underestimated due to the existence of individuals opting not to receive medical care or receiving medical care in non-emergency settings such as urgent care or primary care, particularly for more mild TBIs. (CDC 2015).

The incidence of mTBI makes up a majority of overall TBI occurrence (~80%), with peak incidence occurring between the ages of 15-24 years of age, predominantly due to sports or recreational activities. Athletics also contributes significantly to repetitive TBI (rTBI) (~50%), therefore the occurrence of TBI/mTBI/rmTBI in young athletes represents a significant, vulnerable subset of the population (Ferguson 2021).

2.4 TBI Symptoms, Measurement, and Evaluation

TBI health effects vary based on the severity of initial injury, access to medical and rehabilitative care, and patient characteristics. Sensory impairment, motor dysfunction, cognitive deficits, and emotional instability represent well characterized symptoms of
TBI, with a majority of patients experiencing at least one of the stated health effects in mTBI post-injury (Table 2).

Quantification of TBI severity may be accomplished with a combination of methodologies combining neurologic assessments such as the Glasgow Coma Scale (GCS) (Table 3), with neuroimaging techniques. The GCS is a straightforward evaluation of a patient’s consciousness level by measuring responses to stimuli, with the total score from the eye, motor, and verbal responses used as a prognostic and clinical indicator in addition to the categorical division of TBI with mild injury (13-15), moderate (9-12), and severe (8 or lower) (Sternbach 2000).

The application of complex neurologic imaging techniques is a point of debate as their usage incurs significant costs. The standards to which advanced imaging techniques are applied varies among institutions and areas regarding mTBI as it can be unclear which patients require imaging, potentially incurring undue cost to the individual. More severe injuries tend to be clearer in the necessity for imaging as interventions are more commonly required in such scenarios.

Computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and photon emission computed tomography (SPECT) are used to evaluate TBI patients for injuries requiring neurosurgical intervention (Douglas 2019), with the most common being to CT for its cost effectiveness and general utility in evaluating hard tissue abnormality, acute subarachnoid and parenchymal hemorrhage, and MRI based techniques for their more sensitive detection of minute pathologies associated with mTBI and DAI (Lee 2005). The analysis of white matter degeneration is primarily accomplished via Diffusion Tensor Imaging (DTI) in human patients as
histology observing direct influence of TBI on the brain in vivo using histology or electron microscopy is not a viable approach. DTI is a form of magnetic resonance imaging which uses unequal diffusion of water in the brain in different directions (anisotropic diffusion), caused by the heterogeneity of brain tissue structure and makeup. These differences, caused by cell membranes, myelination and axonal packing, can be used to calculate and track the relative rates of diffusion corresponding to the organization of tissues, as water diffuses more slowly through membranes (O’Donnell 2011) (Figure 2). Once the directionality of many water molecules can be determined, algorithms can summate the values and create a diffusion pattern representative of topography.

Professional diagnosis of TBI is commonly achieved through the consideration of cognitive symptoms and scales (Table 3) combined with circumstantial evidence/subjective symptoms, and while guidelines exist for the administration of imaging techniques to cases of mTBI, most cases forego this type of analysis due to poor cost/benefit ratio (Douglas 2019).

**Biomarkers of TBI**

Blood-Brain barrier (BBB) disruption as a result of mTBI allows the use of blood biomarker analyses to potentially aid in research and clinical settings. Under normal conditions, the BBB restricts the exchange of large molecules (proteins) while allowing the movement of gasses and metabolic waste products through active transport. mTBI and its capacity to disrupt this barrier can result in brain specific proteins being found in peripheral tissues including the blood and cerebrospinal fluid. Analysis of these proteins
and their concentrations using immunoassays has recently been proposed as a clinical diagnostic tool to aid the treatment of TBI (Bouvier 2020).

One such example of a biomarker is Serum Protein 100B (S100B), a dimeric low molecular weight protein belonging to the calciprotein superfamily. Cerebral lesions resulting in the release of S100B from glial cells into the bloodstream can be detected 1 hour post-injury with a half life between 30 and 60 minutes. Although proven to be an effective indicator of mTBI, confounding factors remain in the usage of S100B, namely its ability to be synthesized outside of the central nervous system in peripheral tissues. Melanocytes and lymphocytes express detectable levels of S100B and increased protein concentrations have been observed in athletes, but multiple studies have confirmed its sensitivity for mTBI, indicating the serum concentrations of non-TBI subjects and TBI subjects can be distinguished. Though the US Food and Drug Administration has not approved S100B as a tool in the diagnosis of TBI, European countries regularly utilize the biomarker in clinical practice (Bouvier 2020).

Another promising biomarker, Glial fibrillary acidic protein (GFAP), has been shown to increase in concentration following mild to moderate traumatic brain injury. Specific for brain injury, GFAP shows more favorable protein kinetics than S100B being detectable within 1 hour of injury and reaching a maximum within 20-24 hours of injury followed by a decline over a 72 hour time span (Heubschmann 2020). This longer detection range along with effectiveness in screening for TBI induced abnormalities has led to an FDA approval for GFAP as a consideration in clinical decisions regarding head CT.

Computerized neurologic assessment tools (ex. ImPACT) are becoming increasingly popular in highschool and collegiate athletic settings due to a variety of advantages in
ease of data collection and storage, randomization reducing practice effects, and ability of non-medical personnel to administer training. This type of tool allowing integration of data has demonstrated ability to diagnose concussions and provide prognosis post-mTBI (Fakhran 2013). Further research into the mechanisms surrounding TBI could yield more accurate, available and effective prevention and diagnostic tools.

2.5 TBI research: Animal models

Although mammals closer in size to humans than rats or mice (sheep, pigs, dogs, cats, rabbits) would provide more directly comparable models and are used in some TBI studies, murine and rodent models are overwhelmingly used due to the ease of handling, lower relative cost, and standardized outcome measurements. Tests involving known TBI-induced deficits in humans are mirrored in assessments measuring sensorimotor (cylinder and rotorod, grip strength, forelimb reaching, staircase), cognitive (Morris water maze, freezing response, object recognition), and behavioral (elevated-plus maze, emotional and exploratory activity, open field) outcomes in murine and rodent models (Xiong 2013).

Four main types of injury models are used to analyze the effects of varying severities of brain injury on the subjects; fluid percussion injury (FPI), controlled cortical impact (CCI), weight drop impact acceleration (WD), and blast injury. Each method of administering injury is useful in mimicking human TBI pathologies and demonstrates distinct advantages and disadvantages in terms of mortality, repeatability, variable control, and location (Figure 4).
FPI uses a fluid to transmit force from a pendulum through a reservoir, into the dura exposed through a craniotomy. Historically, lateral FPI (LFPI) is one of the most popular methods used in studying TBI, though due to its local effect causing mostly unilateral damage, midline FPI is becoming more popular in the study of diffuse brain injury occurring during sports or blast injuries.

CCI used a pneumatic or electromagnetic actuator to drive an impactor into the exposed dura. Similar to FPI, CCI requires a craniotomy to expose the dura for insult, but instead of unilateral damage, CCI can induce more widespread damage including acute cortical, hippocampal and thalamic degeneration depending on mechanical factor parameters such as velocity, depth, time of impact and location.

Simple WD models forgo a craniotomy and drop a free falling guided weight onto the skull, whereas Feeney’s WD model impacts the intact dura. Increasing the weight’s mass and drop height induces more severe TBI. Variations of FPI, CCI and WD models are often used to target specific brain regions and mimic injury associated with common human TBI pathologies such as contact sports, and vehicle accidents.

Blast related TBI on the modern battlefield is attracting attention as a major contributor to TBIs.

Information accumulated over the timeframes spanning Operation Iraqi Freedom and Operation Enduring Freedom by the Department of Defense shows that blast related TBI makes up a majority of cases in the pathological distribution of closed head (20%), penetrating (20%), and blast TBIs (60%) in combat zones as opposed to in civilian life where closed head TBI is most common and blast-related injuries are rare. Further
complicating blast-related TBI is its unique damage profile characterized by very short mechanical insult time due to the nature of explosive blasts. Animal models of TBI blast injury include usage of compression driven shock tubes simulating the effects of a blast, and more recently a true blast-induced TBI model in rats.

With FPI, WD and CCI all providing advantages and disadvantages in the reproducibility of conditions and data, ease of use, convenience, damage profile and regions affected, a single model of injury cannot be used to mimic and account for all variables seen in the diverse set of conditions causing TBI in humans, particularly athletic injuries where the variability in conditions surrounding injury are just as diverse and unpredictable as the sports themselves.

While animal models provide some insight applicable to human TBI, limitations exist that prevent a complete 1-to-1 translation of laboratory findings into viable clinical solutions. For example, although broadly similar, differences in non-human mammal brain structure and function including brain geometry, craniospinal angle, gyral complexity and white-to-grey matter ratio contribute to potentially different outcomes in animal/human models. Measurement of physiological variables such as O2, CO2 concentrations, blood pH and pressure, and body/brain temperature is also not standardized and as such not required in many studies despite their importance in injury response. Additionally, the methods of quantifying injury severity in animal models mostly rely on histological evidence and functional tests which can be impacted by the experimental design and mechanical parameters due to the usage of bespoke injury devices. Finally, one of the most glaring discrepancies between pre-clinical research and epidemiological data is the usage of mainly male adult rats in TBI studies which may not
provide a comprehensive understanding of how TBI affects the developing brain and sex-related and activity dependent differences in outcome (Wright 2017, Rubin 2019).

Unlike animal models where histological data is easily accessible post-TBI, the invasiveness of acquiring human brain tissue for analysis relegates histological study of human brain tissues to a post-mortem timeframe. Short term analysis of white matter trauma post-TBI in humans relies mostly upon MRI based neuroimaging such as Diffusion Tensor Imaging (DTI) to analyze changes in the diffusion of water particularly through myelinated axonal bundles, reflecting their integrity (Figure 2). Alterations of fractional anisotropy in the corpus callosum and frontal white matter have been shown following mTBI in adult and pediatric patients, correlating with cognitive and motor post-concussive symptoms and severity (Prins 2010). Evidence supporting white matter as a main contributor and substrate of post-concussive symptoms was also shown by analysis of gray matter partial volume by Messe et al. in 2010. Messe’s group showed no significant differences between “Poor Outcome” and “Good Outcome” groups in terms of gray matter volume post-TBI, suggesting gray matter lesions contribute less to the overall symptoms during the acute stages of injury (Messe 2010).

In a different study utilizing DTI and fiber tracking software to map the damage of mTBI in concussed patients, evidence supporting white matter abnormality correlating with neuro-psychologic abnormalities was found. Rutgers et al. study concluded reduced Fractional Anisotropy present in supratentorial projection fiber bundles, callosal fibers and fronto-temporo-occipital association fiber bundles located in cerebral lobar white matter, cingulum and corpus callosum regions was indicative of mTBI induced damage to these fibers/regions. Interestingly, the time interval in which each patient was studied
bore no relation to the fiber tracking results, potentially suggesting temporal, environmental or genetic factors influencing recovery or lack thereof in this group of individuals studied (Rutgers 2008).

2.6 Long term TBI effects

Myelination necessary for emotional, cognitive and behavioral function relies on the association of oligodendrocytes with axons, both of which are susceptible to TBI and secondary effects (Mu 2019). Evidence supporting demyelination of axons in both mTBI and moderate-severe TBI has been demonstrated in both acute evaluations (Armstrong 2016)(Gold 2018) and in long-term studies (Johnson 2013) in conjunction with persistent inflammation, myelin breakdown, and the axonal accumulation of amyloid-β, caspase-3 and other cellular products (Dent 2015). Some studies have considered this immunocytochemical evidence in supporting the connection between mTBI/rmTBI and Chronic Traumatic Encephalopathy (Bramlett 2015)

2.7 White Matter Injury/ Demyelination

Primary injury to myelinated axons through mechanical force resulting in axonal degeneration may on its own cause demyelination, as the axonal Wallerian degeneration seen distal of the injury site coincides with myelin fragmentation and loss. In the PNS, clearance of these debris are facilitated by Schwann cells, but oligodendrocytes in the CNS characteristically lack an affinity for myelin debris removal which is necessary for axonal regeneration as myelin has been shown to inhibit neurite outgrowth (Vargas 2007).
Oligodendrocytes are susceptible to TBI related secondary trauma, particularly oxidative and metabolic stressors due to their high metabolic demands and low capacity to combat reactive oxygen species. Additionally, release of inflammatory cytokine interferon gamma (IFNγ) has been shown to trigger apoptosis in proliferative oligodendrocyte precursors responsible for migration and repopulation of oligodendrocytes in damaged tissue post-injury. Mature oligodendrocytes have also been shown to undergo apoptosis in the presence of tumor necrosis factor α (TNFα), a cytokine documented in both experimental and clinical TBI models (Dent 2015)(Longhi 2013). Persistent immune activation after rmTBI has been correlated with poorer cognitive/behavioral outcomes and pathology, and could be a major contributor to ongoing demyelination associated with long term deficits (Mouzon 2014). Increased membrane permeability and Ca2+ influx, due to excitotoxic events releasing glutamate and ATP, also may cause apoptosis in oligodendrocytes responsible for remyelination post-injury (Dent 2015).

3. Main Review

Sports related TBI (srTBI) are a major health concern, as estimates suggest between 300,000 and 3.8 million srTBIs occur in the United States per year. Resultant emergency room visits and hospitalizations amount to 500,000 and 60,000 respectively, with an estimated 60-80% of srTBI related emergency department visits involving children/adolescents. Many studies have evaluated the effects of TBI in athletics in adult populations, particularly in professional or collegiate sports, but pediatric srTBI studies are counterintuitively less common when considering participation rates in youth vs professional sports. Not only is epidemiological presence of srTBI relevant, the significance of head injury varies due to physiological differences in adults and children.
influencing developmental capacity and long term implications regarding disability and mortality (Yue 2016).

One of the largest hurdles to overcome in studying srTBI in youth is significant underreporting of injury. For example, amateur male hockey players were found to experience 14 times more concussions than official metrics would suggest (Guenette 2018). Combined with the lack of imaging for athletes sustaining mild TBI where intracerebral bleeding is not suspected, the information available to researchers regarding repetitive mTBI in sports remains largely in animal models. Based on these animal models, the most significant factors contributing to long term chronic dysfunction post-mTBI/rmTBI include persistent neuroinflammatory response, metabolic cascade disruption and chronic demyelination (Shultz 2012, Mierzwa 2015)

Literature has long known repetitive mTBI to be a causative factor in the development of long term neurodegenerative disease such as Chronic Traumatic Encephalopathy, but experimental models in animals have not distinguished the molecular mechanisms behind the development of CTE pathologies observed in humans. For example, Brody et al. 2015 found that in a rmTBI murine model (4 closed head mTBI impacts over 24 hour timeframe), that animals suffered significant injury observable via abnormal silver staining at 1 week, 1 month and 6 months, but no change in phospho-tau-immunoreactivity suggestive of CTE pathology. Other experimental models have shown behavioral deficits accompanied by relatively minor histological abnormalities including tau immunostaining, but distinctly lacking progressive cortical and perivascular tau pathology indicative of CTE in humans (Brody 2015). This evidence suggests that although the long term effects neurodegenerative deficits seen in CTE are related to the
instances of mTBI, molecular responses in the more acute time frame post-TBI combined with genetic predispositions are responsible for a majority of observed non-tau related pathologies. The elucidation of the intermediary or parallel mechanism(s) of transition from short term trauma to long term cognitive deficit would provide an interesting therapeutic target for active treatment and prevention of TBI and non-TBI related neurodegenerative disease.

rmTBI effect on cognition can be described broadly as “additive” in the effect of repeated trauma. Single mTBI studies have characterized the cognitive deficit post-injury often as mild to no change in cognitive function along with the general resolution of any cognitive symptoms generally occurring within several days of injury in animal models and within 10 days of injury in humans (Fehily 2017) whereas rmTBI symptom severity scale differently depending on injury interval and severity.

In a subconcussive (<1.0 atm) fluid percussion injury model, Shultz et al showed that a single mTBI was sufficient to induce a neuroinflammatory response while not disrupting cognitive, emotional or sensorimotor function in rodents measured via Morris Water maze acquisition and reversal training (Figure 6). Acquisition trials measure latency in finding a stationary platform hidden underwater. Repeated blocks (average of two trial times) determine the capacity to recall the position of the platform relative to landmarks. Reversal training moves the hidden platform opposite of where the acquisition platform was placed and determines ability to extinguish memory of the initial acquisition platform position and learn the position of the new platform. Subconcussive and sham rats observed both in short recovery (24 hour) and long recovery (4 weeks) showed no
significant difference in water maze scores but did display significant differences in neuroinflammatory markers (Shultz 2012).

Though neuroinflammation is a common and well documented occurrence found in human TBI patients, knowledge that this pathology may also coincide with a lack of cognitive impairments exposes a fundamental flaw in the measurement and diagnosis of using cognitive measures. For example, athletes cleared by a medical professional post-mTBI for return to play would commonly use diagnosis criteria centered around cognitive and behavioral symptoms which as described by Shultz et al, may not be present when the brain is in a vulnerable neuroinflammatory state due to the initial injury, opening a window for subsequent TBI to produce a neuroinflammatory reaction, potentially jeopardizing white matter integrity.

3.1 Repetitive TBI

Contrasting with single instances of mTBI where the resolution of symptoms occurs in an acute manner and pathology remains static following injury, evidence in rmTBI models suggests subsequent injuries potentiate development of dynamic long term pathologies.

A murine model of closed head injury (CHI) observing changes in behavioral and histological outcomes at up to 18 months post-injury found that repeated injury at a 48 hour interval not only exacerbated symptoms in the acute phase of recovery, but caused persistent pathological abnormalities which at times was separate from motor deficits. Measuring cognitive function through a Barnes maze test administered 4 times a day for 6 days, evaluating the subject’s ability to locate a black box in a target hole, Mouzon’s group observed repetitive TBI (rTBI) groups perform significantly worse than their single
TBI (sTBI) and sham counterparts in both mean distance and latency finding the target hole at all three timepoints (6, 12 and 18 months).

Histological evidence suggesting white matter injury and glial activation was seen at 12 months post-injury in rTBI groups as measured via Luxol-fast-Blue staining Iba-1 and GFAP immunostaining respectively. Thinning of the white matter dense corpus callosum was observed in the sTBI group at 6 months (12% thinning vs sham) remaining relatively static until 12 months (10% thinning vs sham), whereas rTBI groups displayed more severe and progressive degeneration of white matter, thinning 21% vs sham at 6 months post-injury along with a further 5% degeneration between months 6-12 totaling 26% corpus callosum white matter thickness loss at month 12 compared to repetitive shams (Figure 7).

Mouzon concluded that TBI induced, measurable behavioral and neuropathological consequences are dynamic in nature and chronic in scope, particularly for cases of rmTBI as demonstrated in the animal model used. In a separate study, Gold used a similar model of injury to evaluate the effect of a larger number of mTBI insults within a smaller period, shortening the interval between injuries. Gold group showed profound white matter degeneration of the corpus callosum correlating with increased latency in the performance of elevated platform and Morris water maze test, representative of anxiety/risk taking behavior and spatial learning/memory respectively (Figure 8).

The time between injuries is of particular relevance to athletes as recurring or regularly scheduled athletic events provide more opportunities for exposure to TBI. Data on the internal between injuries could further inform return to play guidelines for athletes.
Cognitive deficits increase with decreasing injury interval, shown by Meehan et. al. Demonstrated using a closed head injury (CHI) model inflicting mTBI injury daily for 5 days, weekly for 5 weeks, and monthly for 5 months. The group found that shorter duration of recovery between injuries degraded performance on hidden platform Morris Water Maze trials measuring spatial learning and memory.

Research evaluating different recovery times between administration of rmTBIs further support the notion that the effects of rmTBI are cumulative and shorter recovery between insults increases progressive dysfunction (Prins 2010).

3.2 Adolescent/active animal models

Some of the most at-risk populations for TBI include active adolescent/young adults participating in athletics. While animal studies in adult rats provide some insight, the developmental period of adolescence could change how pathology following mTBI/rmTBI manifests. For example, in an animal study evaluating Brain Derived Neurotrophic Factor (BDNF) increase post-exercise, adults and adolescent subjects showed different expressions which could have the potential to modulate neuronal apoptosis and oxidative damage (Ferguson 2021). The occurrence of injury in sports often corresponds with increased activity levels, which are not represented in many studies using sedentary animals. Ferguson et al. recapitulate these factors in their model using a postnatal day 35 rats due to their periadolescent equivalence in humans. Previous studies have shown that aerobic exercise preceding moderate-severe TBI has neuroprotective effects on blood-brain barrier breakdown, neuroinflammation and motor/memory impairments (Ferguson 2021). In studying exercised adolescent rats,
Ferguson’s group sought to investigate if this neuroprotective effect extended to mild/repetitive TBI as seen in vulnerable adolescent/young adult athlete populations. To mimic the clinical evaluation used for humans such as the Sports Concussion Evaluation Tool (SCAT) which measures symptom intensity, cognition/memory and balance, the group created The Rat Standardized Concussion Assessment Tool (ratSCAT) composed of tasks mimicking human assessment. Beam walking assessing motor function and balance, open field test assessing anxiety symptoms and Novel Object Recognition (NOR) task assessing memory impairment were used as human concussion test analogues. Closed head injury was administered via a pneumatic impactor against the intact skull, a model which was established in previous studies as causing temporary behavioral impairments, physical impairments and metabolic dysfunction. Between injuries was a 24 hour interval, as previous work had shown metabolic recovery from a single TBI by PID 3, whereas injuries occurring within 3 days caused cumulative and prolonged dysfunction (Ferguson 2021).

The results of Ferguson’s molecular analysis indicate that exercised rats displayed higher levels of markers indicative of neuroplasticity and mitochondrial biogenesis that may exert protective function in the event of a TBI. In addition, the rathlete rTBI group did not exhibit memory impairment when compared to the sedentary individuals also receiving rTBI. With a 24 hour window separating two mTBI injuries, cognitive and behavioral analysis indicated that rats allowed to exercise immediately post-injury had reduced social contact time and novel object recognition during later evaluation compared to uninjured and delayed post-injury exercise rathlete peers, but similar motor and balance scores. These findings suggest that a period of inactivity after TBI, followed
by a return to mild aerobic activity may be beneficial to recovery when compared to complete withdrawal from physical activity, or immediate return to activity (Ferguson 2021).

### 3.3 Demonstration of White Matter change in humans

Correlating CT/MRI abnormalities with changes in Fractional Anisotropy indicating white matter damage has been a proven method of analyzing damage post-TBI, but the data associating TBI with outcome measures is mixed. For example, in an analysis of FA measured via DTI in mTBI measuring white matter injury, comparing patient reported symptoms (specifically sleep-wake disturbances) showed a significant positive correlation between high concussion symptom scores and reduced FA in multiple brain regions. Specific regions of interest targeted found that abnormalities associated with symptoms were found in the posterior gray-white matter junction, and primary and auditory cortices including the Wernicke area. Sleep-wake cycle disturbances post-TBI were found to be correlated with parahippocampal region abnormalities which is a region known to be significantly affected in Alzheimer's dementia, in which, sleep disturbance is one of the earliest symptoms to develop over the disease’s progression (Fakhran 2013).

Messe et al utilized DTI to evaluate whether lesions detected correlate with poor functional outcomes in cognitive, emotional and somatic examination in the subacute time frame (up to 4 months post-injury) after mTBI. The group found that poor outcome subjects displayed significantly increased mean diffusivity in white matter (indicative of damage) than good outcome subjects, suggesting that mTBI induced white matter damage/demyelination is a major contributor to pathology commonly seen in human mTBI patients (Messe 2010).
Alternatively, results in a study by Yuh et al. seeking correlation between FA and outcome measures at 3 and 6 month time points in CT/MRI positive (defined as patients with any acute traumatic intracranial lesion; epidural hematoma, subdural hematoma, subarachnoid hemorrhage, contusion, or evidence of traumatic axonal injury and/or depressed skull fracture on either CT or MRI) and CT/MRI negative groups found reduction in white matter FA only in the CT/MRI positive group, which also was found to be a statistically significant predictor of outcome at 3 and 6 months (Yuh 2014).

The consequences of oligodendrocyte apoptosis leading to demyelination and potential axon degeneration are partially caused by the disequilibrium of ionic gradients after demyelination, as the high density of ion channels present at nodes of Ranvier can no longer retain the appropriate compactness in the axonal membrane and fail to exchange ions at correct rates. Mitochondrial dysfunction and the influx of Ca2+ inducing caspase-mediated apoptosis post-demyelination may be responsible for cognitive deficits seen in a chronic TBI timeframe, as the mechanisms to repair such damage require a coordinated effort between axonal transport and repair/oligodendrocyte migration and remyelination. Also complicating the process of recovery is the duality of microglial activation and response to injury. Showing phenotypic change post-injury, resident microglia responsible for clearing debris and local inflammation under normal conditions may unintentionally damage oligodendrocytes through the release of cellular signalling factors. Cytokines released by activated microglia in the acute phase of mTBI recovery such as tumor necrosis factor-α (TNF-α) are known to inhibit oligodendrocyte progenitor cell (OPC) proliferation and differentiation, and induce oligodendrocyte apoptosis. How and when the transition from protective inflammation to destructive inflammation occurs
is still to be determined and is most likely a result of multiple pathways and systems taking input from a variety of environmental and genetic factors (Shi 2016)

### 3.4 Current Management Strategies

Due to the varying nature of mTBI in its occurrence, manifestation and resolution, the treatment received by individuals can vary greatly. In an effort to resolve at least some of the subjectivity in clinical management of pediatric mTBI, the CDC released a publication in 2018 outlining some of the considerations a clinician should take during the diagnosis, prognosis and treatment of injury. These rough “guidelines” provide a framework to introduce uniformity to the management of pediatric mTBI, while still allowing the diverse nature of brain injuries to be evaluated on a case-by-case basis and the direction of post-concussive care to remain at the discretion of each clinician. Topics contained in the aforementioned publication can be found in Figure 10 (CDC 2018).

Therapeutic approaches beyond rest and general rehabilitation have not been shown to provide consistent benefits, as more than 30 clinical trials have not shown any promising candidates due to the variable nature of TBI in terms of injury cause, location, demographic and available care. As of now, management of symptoms and rest are the only universally agreed upon courses of action to address mTBI (NIH 2020).

### 4. Discussion

In the past 30 years, neuroscience has undoubtedly improved its understanding of mechanisms and consequences surrounding TBI, as well as its relevance in the realm of athletics and the significance and danger it may pose to a disproportionately affected group of adolescents/young adults. The biomechanical principles of primary TBI damage
are relatively well understood and the secondary damage mechanisms and cascades are being brought into the light. While general understanding of how mTBI/TBI at point A progresses to symptomatic pathologies at point B, the path or paths along that road from A to B are still being explored. Mechanisms of damage being studied face a particularly challenging conundrum, as the means required to collect the necessary information in sufferers of TBI are limited to non-invasive methods, as invasive methods could potentially cause more acute and chronic damage than the original injury itself.

Diagnostic tools also face issues in terms of their application and effectiveness. As mentioned previously, CT imaging is one of the most commonly used technologies to evaluate TBI patients, but its sensitivity to minute changes as seen in mTBI and secondary injury are limited. DTI, while sensitive for diffuse axonal injury and demyelination, faces challenges of integration into clinical practice and limited database resources as a comparative reference to evaluate individual patients that have not received baseline DTI studies. Biomarkers, while gaining traction as viable methods to indicate CT positive patients (patients which would show abnormalities evaluated by CT) there is only moderate evidence suggesting the correlation between serum biomarker concentrations and functional outcomes. As such, standard clinical practice guidelines may utilize each diagnostic tool as part of a multifactorial approach in cases of TBI due to the weaknesses inherent in each strategy.

Questions that require more immediate attention include; How exactly does age play a role in neurotrauma, and if/how does persistent/repeated damage cause slowing of neurological function and development? What are the differences between males and females in terms of tolerance to TBI and the manifestation of symptoms? The number of
studies involving female subjects are more scarce not only in animal studies but human studies as well, potentially owing to the fact neuroscience research has historically skewed towards study of the male brain, and that regarding the particular topic of TBI, men make up a much larger proportion of the afflicted population. The research into sex-related differences in TBI have also yielded conflicting evidence, with human studies suggesting that females are more likely to experience worse outcomes than males, and animal studies reporting the opposite (Gupte 2019). Long term impact of rmTBI regarding development of neurodegenerative diseases such as CTE and the risk factors involved also pose questions that need answering.

Perhaps the most important part of studying the questions posed above is the challenge of deciphering how each individual factor surrounding a TBI will interact. How will a 10 year old boy playing football compare to an 18 year old girl playing soccer in terms of clinical manifestation of symptoms and their long term potential to develop persistent damage? How should governing bodies address the issue of removal and return to play after an athlete has suffered a concussion? If it is established that males and females indeed to show biological differences in their responses to TBI, will there be different guidelines for each sex? The questions posed here are of course completely hypothetical, with current research barely bridging the gap between cause and effect at the moment, but improvements in medical technology such as higher resolution imaging techniques will yield results in studying this demographic when combined with the increase in general public awareness of acute and chronic impacts of mTBI and rmTBI.

Conclusion
As an athlete myself, I have suffered from concussions and know firsthand the challenges and frustration that comes along with them. What seems like good practice in return-to-play policy can feel like bureaucratic red tape. People that have been tasked with protecting your wellbeing such as coaches, trainers and doctors can become obstacles preventing you from returning to the sport you love so much. I have seen teammates intentionally tank their scores on preliminary concussion examinations so in the event they suffer a head injury and have to take the exam again concussed, they are more likely to pass and be allowed to play. The culture around brain injury in sports, while not as bad as in previous decades where little to nothing was known about TBI, is definitely still not perfect and will continue to drag its feet until research can provide concrete evidence guiding rehabilitation and treatment options in place of current methods.
Key Abbreviations

- TBI - Traumatic Brain Injury
- mTBI - Mild Traumatic Brain Injury
- rmTBI - Repeated Mild Traumatic Brain Injury
- srTBI - Sports related Traumatic Brain Injury
- CTE - Chronic Traumatic Encephalopathy
- DAI - Diffuse Axonal Injury
- AD - Alzheimer’s Disease
- GCS - Glasgow Coma Scale
- MRI - Magnetic Resonance Imaging
- DTI - Diffusion Tensor Imaging
- CT - Computed Tomography
- MWM - Morris Water Maze
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Appendix - Tables and Figures

Figure 1: Distributed and Contact Force profiles

(Hemphill 2015)
**Table 1**: Leading causes of TBI related Emergency department visits from 2002-2010.


<table>
<thead>
<tr>
<th>Mechanism of Injury</th>
<th>ED visits</th>
<th>Hospitalizations</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falls</td>
<td>658,668</td>
<td>66,291</td>
<td>10,944</td>
</tr>
<tr>
<td>Struck by or against an object</td>
<td>304,797</td>
<td>6,808</td>
<td>372</td>
</tr>
<tr>
<td>Motor vehicle traffic</td>
<td>232,240</td>
<td>53,391</td>
<td>14,795</td>
</tr>
<tr>
<td>Assault/Homicide</td>
<td>179,408</td>
<td>15,032</td>
<td>5,665</td>
</tr>
<tr>
<td>Self-inflicted/Suicide</td>
<td>*</td>
<td>*</td>
<td>14,713</td>
</tr>
<tr>
<td>Other</td>
<td>122,667</td>
<td>25,478</td>
<td>4,990</td>
</tr>
<tr>
<td>Unknown</td>
<td>97,018</td>
<td>113,172</td>
<td>0</td>
</tr>
</tbody>
</table>

*Estimate not reported because of small numbers

(CDC 2015)
**Table 2**: Symptoms associated with Traumatic Brain Injuries

<table>
<thead>
<tr>
<th>Physical Symptoms</th>
<th>Cognitive Symptoms</th>
<th>Emotional/Sleep Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>Difficulty concentrating</td>
<td>Irritability</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Difficulty remembering</td>
<td>Mood changes</td>
</tr>
<tr>
<td>Balance problems</td>
<td>Feeling foggy</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Dizziness</td>
<td>Feeling slowed down</td>
<td>Depression</td>
</tr>
<tr>
<td>Vision problems</td>
<td></td>
<td>Emotional lability</td>
</tr>
<tr>
<td>Sensitivity to light/sound</td>
<td></td>
<td>Sleep disturbance</td>
</tr>
</tbody>
</table>

(Corwin 2017)
Table 3: Glasgow Coma Scale - Aggregate score combines eye opening, verbal response and motor response sections. Clinical TBI classification based on score: Mild (14–15); Moderate (9–13) or Severe (3–8)

<table>
<thead>
<tr>
<th>Eye opening</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous</td>
<td>4</td>
</tr>
<tr>
<td>To speech</td>
<td>3</td>
</tr>
<tr>
<td>To pain</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best verbal response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Oriented</td>
<td>5</td>
</tr>
<tr>
<td>Confused conversation</td>
<td>4</td>
</tr>
<tr>
<td>Inappropriate words</td>
<td>3</td>
</tr>
<tr>
<td>Incomprehensible sounds</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Best motor response</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Obey commands</td>
<td>6</td>
</tr>
<tr>
<td>Localizes pain</td>
<td>5</td>
</tr>
<tr>
<td>Withdrawal (normal flexion)</td>
<td>4</td>
</tr>
<tr>
<td>Abnormal flexion (decorticate)</td>
<td>3</td>
</tr>
<tr>
<td>Extension (decerebrate)</td>
<td>2</td>
</tr>
<tr>
<td>None</td>
<td>1</td>
</tr>
</tbody>
</table>

(Sternbach 2000)
Differences in water diffusion rates around axonal membranes allows detection of white matter abnormalities and visualization of TBI induced white matter damage. Water diffuses faster within an axon’s parallel axis, while moving slower in the perpendicular direction through the axonal membrane and myelination. TBI induced demyelination can be observed as the increase in diffusion in the perpendicular direction, indicating a disruption in the membrane normally preventing this perpendicular diffusion.

(O’Donnell 2011)
Figure 3: Post-TBI biomarkers, localization, mechanism of release and detection methods which may provide a useful diagnostic tool guiding the use of imaging methods.

### Biomarkers of mild traumatic brain injury

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>Cell localization in the central nervous system</th>
<th>Pathophysiological mechanism explaining the concentration increase in blood in mTBI</th>
<th>Techniques available for blood testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>S100B</td>
<td>Astrocytes</td>
<td>Release from damaged glial cells</td>
<td>ELISA, ECLIA, LIAl, IRMA, IFMA</td>
</tr>
<tr>
<td>Glial fibrillary acid protein (GFAP)</td>
<td>Astrocytes</td>
<td>Release from damaged glial cells</td>
<td>ELISA, ECLIA, Digital</td>
</tr>
<tr>
<td>Ubiquitin carboxy-terminal hydrolase 1 (UCH-L1)</td>
<td>Neuron (cell bodies)</td>
<td>Release from damaged neuronal cells</td>
<td>ELISA, ECLIA, Digital</td>
</tr>
<tr>
<td>Light and heavy neurofilament (NFL, NFH)</td>
<td>Neuron (axons)</td>
<td>Release from damaged neuronal cells</td>
<td>Digital ELISA, Ella</td>
</tr>
<tr>
<td>Tau</td>
<td>Neuron (axons)</td>
<td>Release from damaged neuronal cells</td>
<td>Digital ELISA</td>
</tr>
<tr>
<td>Heart fatty acid binding protein (H-FABP)</td>
<td>Neuron (cell bodies)</td>
<td>Release from damaged neuronal cells</td>
<td>ELISA, ECLIA</td>
</tr>
<tr>
<td>aH-spectrin N-terminal fragment (SNF)</td>
<td>Neuron (cell bodies)</td>
<td>STNF-145 and STNF-150 are products of the degradation of spectrin after calpain cleavage. The accumulation of these fragments in damaged axons produces an increase in the blood concentration</td>
<td>ELISA</td>
</tr>
<tr>
<td>Neuron-specific Enolase (NSE)</td>
<td>Neuron (cell bodies)</td>
<td>Release from damaged neuronal cells</td>
<td>ELISA, ECLIA</td>
</tr>
<tr>
<td>Myelin basic protein (MBP)</td>
<td>Oligodendrocytes</td>
<td>Release from damaged glial cells</td>
<td>ELISA</td>
</tr>
<tr>
<td>β Trace protein (BTP)</td>
<td>Spinal leptomeninges and pachymeninx</td>
<td>Alteration of the blood-brain barrier</td>
<td>ELISA, Nephelometry Latex assay</td>
</tr>
</tbody>
</table>

ELISA: enzyme-linked immunosorbent assay; ECLIA: electrochemiluminescence immunosassay; IFMA: immunofluorometric assay; IRMA: immunoradiometric assay; LIAl: chemiluminescence immunoassay. Ella (Protein simple*) does immunoassays in a microfluidic Simple Plex cartridge.
Figure 4: Schematic diagrams of murine/rodent TBI injury models. Non-human studies rely on a variety of apparatuses to induce TBI in their animal (often rodent) models depending on the region of study and injury type.

(Xiong 2013)
Figure 5: Normal vs abnormal white matter physiology. Following TBI, traumatic axonal injury and demyelination causes irregularities in white matter. Abnormal remyelination by oligodendrocytes may result in inadequate or excessive myelination post-recovery.

(Armstrong 2015)
Activated microglia/macrophages indicated by CD68+ cells in Short Recovery subjects.

Ipsilateral (I) and contralateral (C) hemispheres. Frontal/hindlimb (FH) cortex, parietal/temporal (PT), perirhinal (PR) cortex. Photomicrographs B/C showing CD68 immunoreactivity in injured groups at different magnifications, and photomicrograph D showing immunoreactivity in uninjured sham groups (Shultz 2012).
Figure 7: Mouzon 2014

Luxol Fast Blue stained myelin indicates rmTBI induces progressive degeneration of white matter in corpus callosum, and persistent activation of microglia (Iba1)/astrocytes (GFAP) suggests continued immunological response.

Mouzon et al. 2014
Mice experiencing rmTBI show significant white matter degeneration and 31% corpus callosum atrophy corresponding with poorer elevated plus maze and Morris water maze scores 2 months post injury. Three dimensional reconstructions based on representative animals. Corpus callosum volume plotted against Elevated Plus and Morris Water maze open arm time and escape latency respectively. Longer latencies suggest increased anxiety-like and risk taking behavior (Elevated plus) and poorer spatial learning and memory recall (Morris water maze).
Figure 9: Meehan et al 2012

MWM hidden trial - 1 month post injury: (Y-axis = escape latency in seconds)

A) 5 injuries, 24 hour interval. B) 5 injuries, 1 week interval. C) 5 injuries 1 month interval

Meehan 2012
**Figure 10:** Categories of CDC guidelines and recommendations for pediatric mTBI.

Each section contains a subject in the chronology of a mTBI which was reviewed, and assigned a level of confidence in the recommendation as to the usage/application of the topic in question.

<table>
<thead>
<tr>
<th>Diagnostic Recommendations</th>
<th>Prognostic Recommendations</th>
<th>Recommendations Related to Management and Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Risk factors for Intracranial Injury and Computed Tomography (CT)</td>
<td>1. General Health care Provider</td>
<td>1. Patient/Family Education and Reassurance</td>
</tr>
<tr>
<td>----------------</td>
<td>---------------------</td>
<td>---------------------------------</td>
</tr>
<tr>
<td>6. Serum Markers</td>
<td>6. Vestibulo-Oculomotor Dysfunction Management/Treatment,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7. Sleep Management/Treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8. Cognitive Impairment Management/Treatment</td>
<td></td>
</tr>
</tbody>
</table>