ABSTRACT
This article provides an overview of the Brown University Traumatic Brain Injury Research Consortium (TBIRC) and summarizes the multidisciplinary basic and clinical neuroscience work being conducted by investigators at Brown University and the affiliate hospitals in association with the Norman Prince Neurosciences Institute (NPNI).

KEYWORDS: Traumatic brain injury [TBI], concussion, biomechanics of head impact

INTRODUCTION
Traumatic brain injury (TBI) has become a health issue of major concern in recent years due to increasing numbers and evidence of long-lasting effects. Between 2000 and 2012 the US military reported more than 250,000 cases of TBI whereas, in the civilian population, there are an estimated 1.7 million cases per year, most of which are classified as mild TBI [mTBI] or concussion.

The Brown TBIRC was established in 2012 at Rhode Island Hospital (RIH) under the NPNI umbrella, uniting basic and clinical neuroscience researchers at RIH, Providence Veterans Affairs Medical Center, Butler Hospital, the Brown Institute for Brain Sciences and Alpert Medical School of Brown University. Members of the consortium consist of a diverse group of clinician scientists (including the Departments of Neurosurgery, Neurology, Psychiatry, Neuroradiology, Emergency Medicine, Orthopedics and Neuropsychology), biomechanical engineers, biostatisticians and basic neuroscientists. TBIRC members are conducting studies to better understand the mechanisms of brain injury, to find methods to identify features that affect prognosis, and to develop treatments for patients with TBI. Linking clinical neuroscience and public health, members of the TBIRC also serve on the State of Rhode Island Governor’s Permanent Advisory Commission on TBI, the Sports Medicine Advisory Committee of the Rhode Island Interscholastic League and have served on the Institute of Medicine’s Committee on Sports Related Concussion in Youth. The following describes several of the research projects currently underway.

MECHANISM OF INJURY
Biomechanics of Head Impact
While concussions are a growing health care concern, the mechanism and the basis for prevention and treatment remain poorly understood. Head acceleration after impact is the primary mechanical factor in concussion injury. However, the relationship between the biomechanics of impact and its clinical effect is unknown. The Head Impact Telemetry (HIT) System is an accelerometer-based head impact monitoring device (Simbex, Lebanon, NH) that

Contact sports: Helmets with special sensors allowed researchers to gather data on the strength, number, and direction of blows to the head in contact sports like football. Data from the sensors shows that running backs and quarterbacks suffer the hardest hits to the head, while linemen and linebackers are hit on the head most often.
allows researchers to record the frequency and severity of head impact sustained by helmeted athletes during play. This provides information toward understanding the biomechanical basis of concussion and repeated subconcussive impacts.

In our approach to understanding the biomechanics of concussions, we have used data collected by the HIT System to quantify head impact exposure, a multifactorial term that includes the frequency, magnitude, and location of head impacts. Our objective is to quantitatively measure head impact exposure in contact-sport athletes, in relation to their head impact mechanism. These data are then correlated with clinical outcome.

Previously, we have quantified and reported head impact exposure based on player position in collegiate football players. In a subsequent study that evaluated impact associated with clinical concussion, we identified a relationship between type of head impact exposure and incidence of concussion. We are now applying this analysis to men’s and women’s collegiate ice hockey to determine the additional role that gender may play in the athlete’s biomechanical tolerance to concussion.

We propose that reducing an athlete’s head impact exposure is a practical approach for reducing their risk for brain injury. In order to investigate strategies for reducing head impact exposure, we developed a tool that synchronized HIT data with game video footage to associate the biomechanics of head impact with specific impact mechanisms (e.g., head contact with the ice in hockey). Using this technique, we have identified the circumstances of play that result in the most frequent or high-magnitude head impact. By quantifying the biomechanics of concussion we have accomplished the first step in understanding concussion injury with practical application to furthering our exploration of early detection and prevention.

**CLINICAL SEVERITY ASSESSMENT**

**Attention Network Task for Acute Concussion Modified**

The development of an easily administered, reliable, and valid measure of mTBI-related attention dysfunction was motivated by a need to understand when U.S. military veterans of Iraq and Afghanistan could be safely redeployed to combat after having sustained mild traumatic brain injury [mTBI]. One such test would also have clear utility and application to the sports arena where augmentation of current return-to-play guidelines would have expected benefit for preventing severe or chronic brain injury.

In order to achieve this goal, investigators at Brown and the Providence VA Medical Center have modified the computer-administered Attention Network Task [ANT], a well-established visual flanker task, to serve as a screening measure for changes in attention during the acute and near-term post-acute period following mTBI. The modified ANT [mANT] includes distracting sounds [e.g., beeps, buzzes] paired with visual stimuli. The sounds are intended to magnify mTBI-mediated attention dysfunction in military, sports, or other highly stimulating situations.

The ANT is a computer task designed to evaluate alerting, orienting, and executive aspects of attention. It requires the participant to rapidly determine the left-right direction of a central arrow surrounded by congruent or incongruent flankers (e.g., ← ← ← ← or ← ← → ←). The arrows are preceded either by no cue, an alerting cue or an orienting cue [indicating where the arrows will appear]. Prior studies show reduced reaction times (RT) for congruent compared to incongruent arrows, alerting cue compared to no cue, and orienting cue compared to alerting cue.

Using mANT, an initial validation study in 20 healthy young adults tested the hypothesis that RT would be longer and accuracy poorer for sound vs. no sound conditions. However, results showed faster RT for sound compared to no-sound conditions with no differences in accuracy. This unexpected result could be due to additional alerting from the second sensory channel [auditory] since the sounds were designed to occur slightly [400 ms] before the visual presentation of the arrows.

This result raised the question of whether the RT enhancement effect of positive sound conditions would be attenuated following mTBI, and thereby serve as a potentially rapid, easily applied measure of post-concussion disability. Early application of this technique to Brown football players diagnosed with sports-related mTBI where mANT was performed within 72 hours of injury showed that the RT advantage for sound compared to no-sound conditions was significantly smaller for the mTBI group compared to the control group. There were no significant group differences in accuracy. These results provide limited initial support for the mANT as a sensitive measure of acute mTBI.

**EFFECT OF CONCUSSION ON THE YOUNG DRIVER**

Participation in high school and collegiate sports is on the rise, with more than 7 million high school students participating in 2005–2006 and almost 385,000 collegiate students participating in 2004–2005. Concussions represented 11.6% of all high school athletic injuries and 5.8% of all collegiate athletic injuries. Concurrently, novice drivers have the highest crash rate per miles driven of any age group, and it is not until age 25 that the rate starts to approach the rate seen throughout most of adulthood.

The combination of inexperience and developmental and structural risk factors contribute to the statistic that motor vehicle collisions are a leading cause of death in this age group in both boys and girls. Young drivers exhibit diminished ability to judge risk and inhibit impulses, have increased distractibility, and an increased propensity towards risky behavior. During the post-concussive phase, there is evidence of a reduction in visual memory, reaction time, impulse control composite score and processing speed. All of these brain functions are used during the act of driving.
It was purported that during the acute post-concussive period, these alterations will translate to deficits in driving ability. In an Australian study, concussed adult drivers demonstrated impaired hazard perception when compared to non-concussed aged matched controls.14,15

We conducted a pilot research study that enrolled male and female collegiate hockey players from Brown University. The athletes underwent pre-season ImPACT testing, Trail-Maker B [TM-B] and Driving Simulator testing. TM-B is an assessment tool that provides information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. It is also sensitive to detecting several cognitive impairments. Following concussion, the athletes repeated both the Driving Simulator and TM-B within 48 hours and then serially until their symptom score and ImPACT tests normalized. Early results of comparison of preseason testing with concussion identified deficits in both the Trail-Maker B and the Driving Simulator sections.

Our intention is to expand our study population to include both high school and additional college athletes in order to better inform driving recommendations for our young drivers who have sustained mild traumatic brain injury.

ASSESSMENT OF MORBIDITY AND PROGNOSIS

Inflammatory Biomarkers for Mild Traumatic Brain Injury

Mild TBI or concussion, which represents the majority of TBI cases, is increasingly being recognized in adolescents,16 and the associated morbidity can be significant in this age group. A substantial subset of these children has delayed recovery, resulting in the loss of productivity and psychosocial distress.17 Compared to adults, adolescents are more susceptible to repetitive injuries and post-concussion syndrome (PCS). Currently, there is no established method for predicting the recovery period and determining the optimal treatment for individual mTBI patients. Certain patient characteristics or symptoms observed at admission appear to be predictive of PCS.18 However, more objective measures would improve clinicians’ ability to provide prognostic information and potentially guide therapy.

There has been a considerable interest in identifying serum biomarkers that would allow for diagnosis and prognosis in neurotrauma. However, defining such biomarkers for mTBI has been particularly challenging.19 Among the potential biomarkers S100B, a predominantly astrocyte-derived protein, has been extensively studied but demonstrates low sensitivity and specificity as a biomarker for mTBI. Neuronal proteins, such as neuron-specific enolase, ubiquitin C-terminal hydrolase-L1, cleaved tau protein, and II-spectrin breakdown product of 145 kDa, were also found to have significant limitations as serum biomarkers in mTBI. It has been generally assumed that the levels of serum biomarkers should reflect the magnitude of damage of neural tissue caused by injury. However, the extent of damage of neural tissue in mTBI is likely to be quite limited, which may explain the low sensitivity of serum biomarkers that have been studied. We are pursuing an alternative approach to identify proteins that are produced in the brain but whose serum levels would reflect functional changes in brain parenchymal cells rather than the cellular damage resulting from injury.

Our studies involve both pediatric (adolescent) and adult populations of mTBI patients, and include control groups of patients with long-bone fractures and healthy volunteers. These investigations focus on inflammatory biomarkers. Although the pathophysiological processes accompanying mTBI/concussion are not fully understood, studies in animal models of mTBI suggest that neuroinflammation plays a significant pathophysiological role in mTBI.20 In this context, it is also important to note that the immature brain likely exhibits a much stronger inflammatory response to injury than the adult central nervous system.21 There is ample evidence of adverse effects of neuroinflammation on various aspects of brain function, which are highly relevant to mTBI and PCS. Neuroinflammation has a detrimental effect on neurogenesis, learning and memory, and appears to play a part in the pathophysiology of depressive disorders.

Our preliminary observations stress the importance of how the collected blood samples are processed. While the serum levels of circulating proteins are commonly assessed, the coagulation process involved in harvesting serum may liberate some proinflammatory mediators that are carried by circulating leukocytes or bound to Duffy antigen receptors expressed on erythrocytes.22,23 For example, we have found that the serum levels of CXCL1, a neutrophil chemoattractant, are considerably higher than those measured in plasma. This indicates that some published data should be evaluated with caution. Our studies have nearly completed enrollment. If our hypothesis is correct, the results may have prognostic potential for mTBI, may assist clinicians in tailoring recommendations to patients, and may provide the mechanistic basis for new therapeutic approaches in mTBI patients.

NOVEL MRI FINDINGS IN COLLEGIATE ATHLETES WITH MILD TRAUMATIC BRAIN INJURY

A team of clinical neuroscientists, radiologists, statisticians and brain imagers at RIH and Brown University is investigating the utility of routine, advanced and novel MR imaging sequences in collegiate athletes for identifying early features that define subjects at risk for long-term sequelae of mTBI. In addition, we are studying subacute functional and microstructural brain MR changes that may correlate with the quality and severity of long-term post-mTBI disability.

To investigate this question we have designed a research trial that enrolls scholastic athletes with sports-related concussion (Glasgow Coma Scale24 of 13-15). 3T-MR imaging is performed at Brown University or RIH within 72 hours of concussion and then repeated three months later. The MR imaging protocol includes standard clinical sequences that...
measure brain anatomy and edema, (T1 {MPRAGE}, FLAIR), as well as newer imaging techniques with improved sensitivity to very small quantities of brain hemorrhage {SWI}, white matter tract integrity {DTI} and cerebral blood flow {ASL}. A novel imaging sequence, developed by researchers at Brown, for quantification and localization of brain myelin {mcDESPOT} is also included in the research trial. Athletes enrolled in the study also complete post-concussive symptom surveys at each imaging time point, and at one month following concussion.

The preliminary findings of routine MR imaging have paralleled existing concussion literature. Standard T1 and FLAIR routine imaging sequences, even at 3T, appear insensitive to the effects of mild traumatic injury and appear to be of little diagnostic value. The high sensitivity heme sequence {SWI} identified punctate deep white matter hemorrhage in a small group of subjects. Although present in subjects with severe acute subjective symptoms, this finding did not affect treatment decision-making or affect long-term outcome.

The early data supports a potential role for cerebral blood flow {CBF} analysis imaging, suggesting regionally altered CBF in the acute post-injury state. Of note, limited recent literature has also identified early-altered CBF in deep grey matter structures following mTBI. We plan to assess the utility of this finding for predicting long-term clinical and structural sequelae.

DTI findings have thus far been consistent with existing literature that demonstrates decreased white matter tract integrity {FA values} in frontal and mesial temporal lobe structures susceptible to head injury, such as the uncinate fasciculus and genu of the corpus callosum. The relevance of these microstructural changes to long-term clinical sequelae is currently being explored.

The preliminary findings of disordered myelin content revealed by mcDESPOT in the chronic post-injury phase have been significant and unexpected. With further exploration using this technique in a larger study population, we hope that it will demonstrate utility for identifying sites of microstructural brain injury, and for furthering our understanding of myelin repair and its potential impact on long-term disability.

INFLUENCE OF COMORBID DISORDERS AND POSSIBLE TREATMENTS FOR PATIENTS WITH MTB

A focus of study in the RIH division of neuropsychiatry and behavioral neurology is the relationship between mTBI seizures, and psychiatric comorbidity. Patients with mTBI have seizures that are not always epileptic. In fact, mTBI appears to be a significant risk factor in patients with psychogenic nonepileptic seizures {PNES}, and is associated with increased psychiatric co-morbidity, symptom severity, poor functioning and increased disability.

In a study that compared patients with PNES and TBI to those without TBI, we found that 45% of patients with PNES also had TBI, and 73% of those TBIs were mild TBI. The study revealed that if a patient had both PNES and TBI, the combination resulted in 2.75 odds increase of having posttraumatic stress disorder {PTSD} and triple the odds increase of having a history of trauma abuse. This finding illustrates the importance of the ‘double hit’ of emotional and physical traumatic experiences that may occur with abuse or a head injury, commonly found in the PNES population.

This study shows that TBI and PNES are significantly associated with a cluster of diagnoses including depression and PTSD, personality, or trauma and abuse history, all of which may affect functioning. Developing appropriate protocols to more accurately diagnose these patients is the first step to ensure proper care.

The neuropsychiatric approach to brain-behavior disorders research is being applied to other studies discussed in this article, including a pilot study of neuroimaging, cognitive measures and psychiatric symptoms in college athletes who sustained concussion. Given the significant numbers of veterans with TBI, a study proposal of mTBI diagnosis and treatment in veterans at the Providence VA Medical Center has been recently submitted. Ultimately, the goal of the division of neuropsychiatry is to develop prevention strategies and clinical treatments for patients with mTBI.

References
11. Shope JT. Influences on youthful driving behavior and their


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Disclosures

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