Brain Imaging and Behavior (2012) 6:255–282
DOI 10.1007/s11682-012-9162-7

mTBI SPECIAL ISSUE

Embracing chaos: the scope and importance of clinical and pathological heterogeneity in mTBI

Sara B. Rosenbaum · Michael L. Lipton

Published online: 2 May 2012

Abstract Mild traumatic brain injury (mTBI) manifests a wide array of clinical features, indicating great heterogeneity of its underlying pathologic features. mTBI diversity is related to pre-injury inter-individual differences and differences in the characteristics of each injury. This review summarizes key features of mTBI patients, their injuries and outcomes to give context to the scope of complexity inherent in this disorder. These differences are underscored by heterogeneity in postmortem pathology and in vivo imaging studies. Recognition, understanding and accounting for disease heterogeneity in mTBI are needed to enhance diagnosis and patient management, as approaches that do not account for inter-individual variation in pathology and patient characteristics relevant to real-life clinical trial participants, may entirely miss therapeutic targets. Refining our approach to TBI diagnosis, in light of inter-individual differences, can facilitate the development of effective prognostic tools and algorithms. New paradigms, which embrace heterogeneity of mTBI, in both preclinical and clinical investigation as well the appreciation of this variability in clinical care, offer much promise for enhancing outcomes and mitigating the burden of mTBI on its victims.

Keywords Mild traumatic brain injury (mTBI) · Heterogeneity · Biomechanics · Diffusion tensor imaging (DTI) · Post-concussive symptoms (PCS)

S. B. Rosenbaum · M. L. Lipton (✉)
The Gruss Magnetic Resonance Research Center, Departments of Radiology, Psychiatry and Behavioral Sciences and The Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY 10461, USA
e-mail: michael.lipton@einstein.yu.edu

Introduction

Mild traumatic brain injury (mTBI) manifests as a wide array of clinical features, indicating great heterogeneity of its underlying pathology. Diversity of mTBI should be expected due to pre-injury inter-individual differences and differences in the characteristics of each injury. Yet, studies of mTBI tend to consider groups of patients meeting certain diagnostic criteria as victims of a monolithic disease process. The myriad candidate mechanisms implicated in the pathogenesis of TBI provide a strong basis for the variable manifestations of injury pathology observed in vivo with imaging studies and at autopsy. A central clinical dichotomy dramatically underscores the variability seen in mTBI patients: most patients experience excellent recovery after mTBI, with no persistent clinical evidence of injury, while approximately 30 % suffer persistent and often life changing clinical sequelae (Alexander 1995). The striking difference in outcome between this "miserable minority" and the fortunate majority who do extremely well implicates significant differences between mTBI patients. The study of mTBI is further encumbered by its various definitions (Table 1); for example, the definition of post-concussive syndrome differs between the ICD-10 and DSM-IV (Barlow et al. 2010; Ruff 2011; Yeates 2010). This review will summarize key features of mTBI patients, their injuries and outcomes to give context to the scope of the complexity inherent in this disorder. Recognition, understanding and accounting for disease heterogeneity in mTBI are needed to enhance diagnosis and patient management. Furthermore, as recent reports have identified patient selection as a potential explanation for failure of most recent treatment trials in TBI (Margulies and Hicks 2009), disease

Table 1 Various definitions for mTBI and synonyms thereof (mild head injury, mild closed head injury, and concussion) and salient features of each definition. Note that some choose to sub-classify mTBI according to severity or risk (Carroll et al. 2004; Esselman and Uomoto 1995; Kelly and Rosenberg 1997; McCrory et al. 2009; Servadei et al. 2001; Shukla and Devi 2010; Vos et al. 2002; Williams et al. 1990) min. = minutes; h = hours

Organization	Term and definition	Unique features of definition
Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehab Medicine (1991)	**Mild Traumatic Brain Injury:** At least one of the following criteria: Any period of LOC <30 min. and GCS 13–15 after this period of LOC Any loss of memory for events immediately before or after the accident, with PTA <24 h Any alteration of mental state at the time of the accident Focal neurological deficit that may/may not be transient	• Broad definition • Does not identify subgroups • Includes persistent neurological deficits
Centers for Disease Control and Prevention	**Mild Traumatic Brain Injury:** GCS 13–15 One or more of the following conditions subsequent to brain injury: 1. Transient confusion, disorientation or impaired consciousness 2. Amnesia near time of the injury 3. LOC <30 min. 4. Neurological or neuropsychological problems (seizures, irritability, lethargy, vomiting, headache, dizziness, fatigue or poor concentration)	• Broad definition • Does not identify subgroups • Does not specify duration of PTA
WHO Collaborating Centre for Neurotrauma Task Force on MTBI	**Mild Traumatic Brain Injury:** Acute brain injury resulting from mechanical energy to the head from external physical forces. Criteria for definition include: One or more of the following: 1. Confusion or disorientation 2. LOC <30 min. 3. PTA <24 h 4. Other signs of transient neurological abnormalities (focal signs, seizure, intracranial lesion not requiring surgery) And: GCS 13–15 after 30 min. post-injury or later **Manifestations of mTBI must not be due to drugs, alcohol, medications, other injuries or treatment for other injuries, other problems or penetrating craniocerebral injury.	• Broad definition • Does not identify subgroups • Describes neurological abnormalities as 'transient' only • Excludes cases where manifestations might be due to other causes
Neurotraumatology Committee of the World Federation of Neurosurgical Societies	**Mild Head Injury:** GCS 14–15 *Low Risk*: GCS 15, no history of LOC, amnesia, vomiting or diffuse headache *Medium Risk*: GCS 15, one or more clinical symptoms (LOC, amnesia, vomiting or diffuse headache) *High Risk*: GCS 14 or GCS 15 with skull fracture or neurological deficits or one or more risk factors (coagulopathy, drug or alcohol consumption, previous neurosurgical procedures, pre-trauma epilepsy, age >60) +/− clinical symptoms	• Excludes patients with GCS 13 • Includes patients without LOC/PTA • Considers clinical symptoms, skull fracture, neurological deficits, and risk factors for risk stratification
European Federation of Neurosurgeons	**Mild Traumatic Brain Injury:** *Category 0*: GCS 15, no LOC, no PTA, no risk factors *Category 1*: GCS 15, LOC <30 min., PTA <1 h, no risk factors (i.e., unclear accident history, continued PTA, retrograde amnesia >30 min., trauma above clavicles, severe headache, vomiting, focal neurological deficit, seizure, age <2, age >60, coagulation disorder, high-energy accident, intoxication with alcohol/drugs) *Category 2*: GCS 15 and risk factors *Category 3*: GCS 13–14, LOC <30 min., PTA <1 h, with or without risk factors	• Sub-classification according to GCS, LOC, PTA and risk factors • Accounts for several pre-morbid risk factors • PTA <1 h (most definitions specify PTA <24 h)
Williams et al. 1990	**Closed Head Injury** *Complicated Mild Closed Head Injury*: Initial GCS 13–15	• Distinction between those with imaging findings secondary to trauma and those without

Table 1 (continued)

Organization	Term and definition	Unique features of definition
	Imaging evidence of focal brain lesion, depressed skull fracture, or both *Uncomplicated Mild Closed Head Injury*: Initial GCS 13–15 Normal CT scan and either a normal skull x-ray or an abnormality limited to a linear or basilar skull fracture	
American Academy of Neurology, Colorado Medical Society Guidelines	**Concussion:** *Grade 1*: 1. Transient confusion 2. No LOC 3. Concussion symptoms or mental status abnormalities on examination resolve in <15 min. *Grade 2*: 1. Transient confusion 2. No LOC 3. Concussion symptoms or mental status abnormalities on examination last >15 min. *Grade 3*: Any LOC, either brief or prolonged	• Sub-classification according to presence of LOC and duration of concussion symptoms • Does not specify GCS • Does not specify duration of LOC
Concussion in Sports Group (2009)	**Concussion:** Complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. These features include: 1. May be caused by either direct blow to the head, face neck or elsewhere on the body with an "impulsive" force transmitted to the head 2. Typically results in the rapid onset of short-lived impairment of neurologic function that resolves spontaneously 3. May result in neuropathological changes but the acute clinical symptoms largely reflect a functional disturbance rather than a structural injury 4. Results in a graded set of clinical symptoms that may or may not involve LOC. Resolution of the clinical and cognitive symptoms typically follows a sequential course however it is important to note that in a small percentage of cases, post-concussive symptoms may be prolonged 5. No abnormality on standard structural neuroimaging studies	• Includes mechanism of injury as part of definition • Excludes cases with abnormalities on neuroimaging

heterogeneity must be acknowledged in order to advance treatment.

The substrate: preinjury factors

Premorbid factors including, but not limited to age, gender, IQ, socioeconomic status, ethnicity, education, genotype, psychiatric history, prior head injury, substance abuse and anthropometrics vary greatly across mTBI patients. Thus, the unique features of each injury (see: THE INJURY, below) are superimposed on a unique substrate, lending a unique signature to the ultimate clinicopathological endpoint of each mTBI.

Age contributes to variable mTBI outcomes

mTBI prevalence has a bimodal distribution, with peaks at 15–24 and in those older than 65 (Abdel-Dayem et al. 1998; Kraus and Nourjah 1988; Mosenthal et al. 2004; Shukla and Devi 2010; Stapert et al. 2006; Sterr et al. 2006). Children and young adults have longer recovery times (Field et al. 2003) and are more likely to exhibit persistent symptoms (Blinman et al. 2009; Grady 2010; Maddocks et al. 1995) than older adults. Moreover, the effects of repeat concussion on executive function are more pronounced in younger than in older athletes (Wall et al. 2006; Zappala et al. 2011). Even among children, age influences outcomes. Taylor et al. showed that in the aftermath of mTBI, older children are more likely to have higher self-ratings of cognitive post-concussive symptoms (PCS) than are younger children (Taylor et al. 2010). In 18-year-olds with remote history of head injury, Teasdale showed that history of a single, mild head injury portends poor performance on cognitive testing only when concussion was sustained between the ages of 12–17, but not younger (Teasdale and Engberg 2003).

Several hypotheses have been advanced to explain increased vulnerability to mTBI in the young, including incomplete myelination, greater head-to-body ratio, and thinner, more compliant cranial bones (McKeever and Schatz 2003; Niogi and Mukherjee 2010). The developing brain is also more sensitive to glutamate-mediated N-methyl-d-aspartate (NMDA) excitotoxic brain injury, and may therefore be at greater risk from excitatory amino acid surges, which occur after TBI (Grady 2010; Field et al. 2003). Cerebral swelling is more diffuse and prolonged in children, precipitating ischemia and intracranial hypertension (Field et al. 2003; Meares et al. 2008; Niogi and Mukherjee 2010). Finally, childhood concussion might lead to impaired plasticity and development (Meares et al. 2008; Zappala et al. 2011).

Elderly TBI patients suffer worse outcomes after TBI in general and mTBI in particular (Stapert et al. 2006; Mosenthal et al. 2004; McCauley et al. 2001). Those over 65 are more likely to develop traumatic hematoma, have longer hospital stays, be permanently disabled and have lower Functional Independence Measure and Glasgow Outcome Score Extended (GOSE), (Stapert et al. 2006; Mosenthal et al. 2004; Vickery et al. 2008; Jacobs et al. 2010). Patients over 50 with diffuse axonal injury (DAI) demonstrate poorer outcomes (Cordobes et al. 1986). Old age is a risk factor for delayed return to work after mTBI (Paniak et al. 2000) and is an important determinant of the effects of alcohol on mTBI outcomes (Allen et al. 2009). Age-based variation in outcomes implicates age-based variation in mTBI pathology, which must be carefully considered.

Women suffer more (or say more?) after mTBI

Women have greater likelihood of persistent post-concussive syndrome (Meares et al. 2008) at 1 month (Bazarian and Atabaki 2001), 3 months (Dischinger et al. 2009; McCauley et al. 2001), and 1 to 5 years after mTBI (Bohnen et al. 1994). High prevalence of PCS in pediatric and adult women is particularly true for somatic symptoms (Farace and Alves 2000; Taylor et al. 2010). Men, on the other hand, are less likely to seek treatment (Demakis and Rimland 2010) and to report persistent symptoms at 3 months after injury (Bazarian et al. 2010; Demakis and Rimland 2010) and are more likely to have returned to work at 3 months after injury (Bazarian et al. 2010). Women are more susceptible to sports-related concussion than men (Dick 2009) and, in the event of concussion, are more likely to self-report mild concussive symptoms and show greater decline from baseline on neurocognitive testing (Covassin et al. 2006; Grady 2010).

Reporting bias is one explanation for gender differences, as women report symptoms more readily than men (Bazarian et al. 2010). However, various aspects of gender differences may explain outcome differences, including features such as IQ, family function, problem-solving skills, education, employment and others. Bilaterally distributed brain function, more common in women, may increase the likelihood that any cognitive domain will be affected in a woman sustaining mTBI (Farace and Alves 2000). Reproductive status may underlay gender differences in mTBI outcomes and may have important therapeutic implications in the use of progesterone, for example, as a therapeutic agent in TBI (Stein and Hoffman 2003).

Baseline functioning: psychopathology, personality traits and coping

The potentially confounding and compounding effect of pre-morbid psychiatric disease on mTBI outcome is perhaps best highlighted by the fact that psychiatric disease is often an exclusion criterion in studies of mTBI outcome and diagnosis. Pre-morbid psychiatric disease, however, might increase the likelihood of an mTBI event (Whelan-Goodinson et al. 2009). Pre-morbid antisocial personality disorder and conduct disorder are associated with increased risk for mTBI (Vanderploeg et al. 2007). Several studies have demonstrated that pre-morbid psychiatric disease might also increase the likelihood of adverse outcomes in the aftermath of mTBI. Pre-injury stress, psychological factors, and psychiatric disease are significant predictors of post-concussive syndrome (Dischinger et al. 2009; Kashluba et al. 2008b; Luis et al. 2003; McCauley et al. 2001; Meares et al. 2008; Ponsford et al. 2000) and decreased likelihood to return to work after mTBI (Vanderploeg et al. 2003). It is possible that pre-injury psychiatric disease increases the likelihood of post-injury emergence of PCS and cognitive dysfunction, rather than entirely accounting for these symptoms. Pre-existing affective disorder, for example, does not account for subjective complaints and neuropsychological outcomes after mTBI (Cicerone and Kalmar 1997; Mooney and Speed 2001).

Personality influences coping mechanisms and thereby outcomes after mTBI. Overachievers, perfectionists, and dependent personalities tend to have a more complicated recovery process (Mooney and Speed 2001). Thus, for instance, overachievers tend to return to work before sufficient cognitive recovery has taken place, and are more likely to conceal symptoms from healthcare workers. On the other hand, other personality types may eschew social and professional responsibilities in the wake of the injury (Gronwall 1991). Personality features such as narcissism, borderline personality trait, perfectionism and dependency can increase the likelihood of adverse outcomes (Ruff et al. 1996).

A large body of evidence thus implicates pre-injury psychological health in the ultimate outcome after mTBI. These unique characteristics of the patient need to be considered in assessing prognosis of mTBI. Additionally, because several common psychiatric disorders (e.g., depression and anxiety)

are common consequences of mTBI, the contribution of pre-injury status to psychiatric outcomes after mTBI must be considered.

Exogenous influences on heterogeneity: substance use, abuse, and dependence

More than 1/3 of patients hospitalized with brain injuries are intoxicated at time of admission and 44–66 % have history of alcohol abuse (Corrigan 1995; De Guise et al. 2009; Lange et al. 2007; Tait et al. 2010). Demographic features associated with alcohol use are also important to brain injury outcomes, including lower educational attainment and socioeconomic status, additional substance abuse, psychopathology and prior head injuries (Corrigan 1995). Alcohol may contribute to the evolution of mTBI pathology through a variety of mechanisms including hemodynamic and respiratory depression, increased blood clotting time, blood brain barrier impairment, cerebral atrophy and increased risk for development of hematomas as well as the increased likelihood of co-morbid psychiatric disease and malnutrition (Allen et al. 2009; Kelly et al. 1997; Lange et al. 2007). Severity and chronicity of alcohol use, abuse and dependence will vary among patients, further contributing to mTBI heterogeneity.

Preinjury alcohol use is associated with worse TBI outcomes, including abnormal CT scan at injury (Ruff et al. 1990) and poorer neuropsychological performance at 1 month and 1 year post-injury (Corrigan 1995). Although history of alcohol use consistently portends worse outcomes in mTBI, the literature on intoxication at time of injury is less conclusive (De Guise et al. 2009; Lange et al. 2007). Some have suggested that alcohol may be neuroprotective in the setting of mild, moderate and severe TBI (Jacobs et al. 2010; Tureci et al. 2004), while others report a greater likelihood of adverse outcome (Corrigan 1995; De Guise et al. 2009; Kraus et al. 1989; Lange et al. 2007). Family history of alcohol abuse doubles the incidence of TBI, even if the patient himself is not an alcoholic. Genetic and personality factors influencing neuropsychological performance, increased injury diathesis, and penchant for alcoholism, such as impulsivity and hyperactivity, might be at play (Alterman and Tarter 1985). Post-injury alcohol and substance use also diminishes recovery, decreases the benefit of rehabilitation efforts, and increases risk of seizures after mTBI (Kolakowsky-Hayner et al. 2002).

Co-morbid pre-injury alcohol abuse may be difficult to disentangle from the effects of other substances (De Guise et al. 2009). Marijuana is the most commonly reported substance used by victims of TBI, followed by polysubstance abuse, cocaine, and heroine (Kolakowsky-Hayner et al. 2002). Premorbid substance abuse is a significant predictor of poor post-injury living and employment status (MacMillan et al. 2002). When used shortly before trauma, recreational drugs have been shown to potentiate neuropsychological impairment following TBI (Kelly et al. 1997). Use of analgesics prior to injury is associated with increased symptoms at 3 months post-mTBI, as well as missed work and activities (Bazarian et al. 2010; Kashluba et al. 2008b).

The association of substance use and abuse with mTBI and its adverse outcomes is clear and will inevitably lead to variation in injury severity, likely dependent on the interaction of exposure severity and other injury and patient factors. However, the mechanisms underlying this phenomenon are not clear; it could be due to substance-using patient characteristics or a direct impact on pathophysiology.

Programmed vulnerability? Genotype and the impact of the ApoE ε4 polymorphism

ApoE ε4 (E4) transgenic mice exhibit greater neuroinflammation, glial activation and neuronal injury than controls (Zhou et al. 2008). Sports concussion has been linked to derangements in the promoter region of APOE (Terrell et al. 2008; Tierney et al. 2010), supporting the relevance of APOE to mTBI. A robust literature shows that the E4 polymorphism confers excess risk of poor outcome after TBI (Ariza et al. 2006; Teasdale et al. 1997; Zhou et al. 2008). Literature on mild TBI is more sparse and inconsistent, with various studies indicating that E4 confers no risk (Chamelian et al. 2004; Moran et al. 2009; Sundstrom et al. 2004), excess risk (Liberman et al. 2002; Moran et al. 2009), or even protects against adverse mTBI outcomes (Pruthi et al. 2010). The effect of E4 may be related to time after injury; Moran et al. demonstrated that pediatric mTBI patients with E4 are more likely to have lower acute scores on the Glasgow Coma Scale (GCS), but ultimately do not differ from controls in terms of PCS and performance on neuropsychological testing at long-term follow-up and, in fact, those with E4 have better performance on tests of constructional skill (Moran et al. 2009 Clin 100). These mixed results could be due to methodological factors, but also may be a clue to further heterogeneity in the evolution of mTBI pathology (Moran et al. 2009), which likely depends on additional, perhaps epigenetic factors.

Resiliency in the face of mTBI: pre-injury intelligence and brain reserve capacity (BRC)

Reserve capacity describes how well an individual can respond to a neurological insult—whether in terms of physical brain structure or functional capacity (e.g., cognitive reserve capacity), that is the efficiency with which an individual utilizes the neurological substrate (Fay et al. 2010). Pre-injury intelligence can be estimated using the Wide Range Achievement Test-Revised (WRAT-R) Reading assessment (Johnstone et al. 1995), educational attainment or IQ. The wide variation among mTBI subjects in education and IQ may thus directly impact heterogeneity of cognitive outcomes

after injury. For instance, pre-injury IQ is a significant predictor of acute concussive symptoms in an adult mTBI population (Meares et al. 2008), as well as of PCS at 1 month, 3 months, and 12 months post-injury in a pediatric population of complicated and uncomplicated mTBI (Fay et al. 2010). Higher intelligence predicts increased likelihood of return to full-time work after mTBI (Vanderploeg et al. 2003), and higher education level is associated with better early functional status in the aftermath of mTBI (Vickery et al. 2008). As with other pre-injury factors, interaction between brain reserve capacity and other features is also important. For instance, it is hypothesized that the link between substance abuse and poor mTBI outcomes is due to drug effects on brain reserve capacity (MacMillan et al. 2002). Variable reserve capacity across patients will affect outcome directly, as above, but also introduces the possibility that impairment may be missed or misattributed. For example, very high functioning patients may still excel on testing despite a significant decrement in their functional capacity.

Repetitive insult: the role of prior TBI on recovery after subsequent injury

It is widely held that successive brain injuries lead to a cumulative effect that is greater than would be expected due to entirely independent injuries. Studies have demonstrated this effect in terms of both post-concussive syndrome as well as cognitive outcomes (Ponsford et al. 2000; Teasdale and Engberg 2003). Prior head injury thus adds an additional feature to the ultimate variability, which will be seen when examining pathology and performance after mTBI (see Baugh et al. 2012). The number, chronicity and frequency of prior injuries remain areas almost entirely unexplored, but a potential source of great heterogeneity among patients.

The impact of multiple injuries is particularly relevant to sports, where players may experience numerous concussive and subconcussive injuries over their years of play at a wide range of intervals and severities. Some sports, such as boxing and soccer, may be particularly likely to result in numerous blows to the head and others, such as football and hockey, may be more likely to entail less frequent, but more severe impacts. Athletes with history of three or more concussions are more likely than those with no prior history of concussion to experience acute symptoms of anterograde amnesia, confusion, and loss of consciousness (LOC) (Collins et al. 2002), to incur longer recovery times after acute injury (Covassin et al. 2008; Guskiewicz et al. 2003; Iverson et al. 2004), to suffer worse long-term outcomes (Wall et al. 2006), to have increased P3 event-related potential latencies to visual stimuli at chronic time points (Gaetz et al. 2000), and ultimately to experience a repeat concussion (Guskiewicz et al. 2003). As baseline deficits in executive functioning and speed of information processing, self-reported symptoms, and learning disabilities have been shown to be greater among those with history of two or more concussions (Collins et al. 1999), individuals experiencing a repeat injury are more susceptible to PCS and neuropsychological deficits because of differences in baseline status. An additional source of spurious heterogeneity in outcomes may relate to the variable reliability of symptom reports and cognitive assessments in athletes who may be highly motivated to minimize displays of impairment in an effort to return to play. The difficulty may similarly be pertinent to combat settings.

A conducive setting for recovery? Social and financial factors

Numerous social factors may intrinsically modulate mTBI outcomes as well as present, on certain domains, potential sources for artifact and bias in the assessment of mTBI patients. Poor social support is a risk factor for persistent postconcussional disorder and depression 3 months after mTBI (McCauley et al. 2001) and social support affects quality of life and likelihood of return to employment 12–24 months post-TBI (Webb et al. 1995). Underscoring the protective role of close social support, those who are unmarried are more likely to have persistent symptoms at 3 months post-injury (Ponsford et al. 2000). Patients with chronic symptoms after mTBI have experienced twice as many adverse life events as have those with remission of symptoms (Fenton et al. 1993) and patients with history of pre-injury life stressors are more likely to have more severe symptoms at 3 months after mTBI (Kashluba et al. 2008b). Social support is particularly important in children, for whom pre-injury family functioning has been shown to affect outcomes in mTBI (Yeates 2010).

Race and ethnicity are related to mTBI outcomes as well. In the United States, mTBI is more common among Native Americans/Alaska Natives and non-Hispanics than it is among Hispanics (Bazarian et al. 2003, 2005). Race is an important factor in return-to-work outcomes (Vanderploeg et al. 2003), as is ethnicity, with Hispanics less likely to develop persistent postconcussional disorder (McCauley et al. 2001). Although minority status has not been shown to impact recovery in terms of mobility and daily living, it has been shown that, in the long-term, minorities have more difficulty with community re-integration (Rosenthal et al. 1996).

Economic status is important to outcome after TBI. Those unable to afford healthcare report lower quality of life and less improvement in functional independence at 12–24 months post-injury (Webb et al. 1995). In a study comparing mild, moderate and severe TBI outcomes between high-income and low- and middle-income countries (LAMIC), outcomes after severe TBI were better in high-income countries, but mild and moderate TBI resulted in less post-injury disability in

LAMIC. This might be explained by the absence or lesser extent of social welfare programs in LAMIC, so that individuals are more inclined to return to work even if not medically prepared to do so (De Silva et al. 2009). Financial issues are also important insofar as they pertain to secondary gain (disability, litigation, workman's compensation), as it might alter the validity of post-injury functional assessment (Binder et al. 1993; Suhr et al. 1997). However, other studies have found that the effect size of litigation on persistent symptoms is not eliminated when symptom validity indices are applied (Belanger et al. 20055 clin 126), or that there is no association between involvement in litigation, receipt of insurance payments and persistent PCS at 3 months post-injury (Bohnen et al. 1994; McCauley et al. 2001). Reports on secondary gain have principally addressed the possibility that outcome assessments might not accurately reflect true functional capacity. We can also question whether the stress of involvement in litigation and other socioeconomic issues during the acute and subacute periods after mTBI adversely impact recovery or the evolution of secondary injury, even at the level of pathophysiology. Further specific study would be required to address this possibility.

Target of impact: anthropometric features underpin biomechanical heterogeneity

Differences in the anatomy and biomechanics of the human skull and brain add additional inter-individual differences which can impact injury severity and extent. Studies attempting to determine impact thresholds for concussion, based on variables such as angular acceleration, linear acceleration, location of impact and impact duration are based on study of uniform models, either anthropomorphic test dummies, human head and neck models (Kleiven 2003; Newman et al. 2000; Pellman et al. 2003) or averaged variables across a population of players in a particular sport (Greenwald et al. 2008; Pellman et al. 2003; Reed et al. 2010). However, it is precisely differences in anthropometry that can affect the biomechanics of a concussion and create variability of mTBI. For example, the infant skull differs from that of the adult in that it is made of multiple plates, with open sutures that close at various time-points. The majority of skull mass is not attained until 5 years of age (Yoganandan et al. 2009). Larger brains are more vulnerable to injury at lower levels of angular velocity and acceleration (Ommaya et al. 2002), and the presence of atherosclerosis can promote tearing of vascular structures (King et al. 2011). Head impact studies conducted using 5th, 50th and 95th percentile Hybrid III dummies have demonstrated different injury criteria values depending on dummy percentile, further highlighting the importance of individual differences in head size to the biomechanics of head injury (Derosia et al. 2004). In the sports literature, neck thickness has been shown to be important in determining head acceleration, change in velocity and displacement during head impact (Viano et al. 2007). Additionally, certain brain structures are particularly susceptible to TBI. Frontal and temporal white matter, fornix, midbrain, hippocampus, corpus callosum and thalamus are thought to be vulnerable to mTBI due to their relationship to the bony skull and other neural soft tissue structures (Bigler and Maxwell 2011; Viano et al. 2005). Ultimately, the combination of a sufficient degree of force at a particular brain location provides a requisite, though perhaps indeterminate, threshold for injury. Still, necessary pathomechanisms (see below) must come into play for injury pathology to evolve and lead to adverse functional outcomes.

The insult: variability in injury mechanism, pathomechanisms and pathologic outcomes

Context and mechanism of injury have important relevance to pathology and outcome after mTBI. Figure 1 divides the populations studied in the mTBI literature according to mechanism of injury, in both adults and children. Between studies, there is a wide range in proportion of total mTBI cases attributable to a particular mechanism. Fall, sports concussion, assault, motor vehicle accident, or combat injury each represents a unique injury type (Pertab et al. 2009), and can be further divided into numerous subgroups. For example, motor vehicle crashes may cause head impact as well as "whiplash" type acceleration injury without impact; combat mTBI may entail direct impact to the head as well as blast overpressure mechanisms of injury among others. Studies that aggregate multiple subgroups will be insensitive to differences that are a function of mechanism. On the other hand, studies focusing narrowly on one injury mechanism may not be generalizable to other mechanisms. Inter-subject variation in physical characteristics of the head, brain and body further multiply the range of possible brain-level injuries to the point where each patient is likely to experience a truly unique mechanism of brain injury at the tissue level.

Research studies typically focus their investigation on a specific biophysical injury profile. Such approaches are understandable in experimental studies, where highly reproducible models are desirable as they allow specific conclusions to be reached, unimpeached by confounding factors. For example, some studies look only at translational acceleration, whereas others look only at rotational acceleration (Kleiven 2003). However, real-life injuries entail simultaneous and sequential acceleration in multiple directions and at multiple angles of rotation. Injuries have also been categorized as impact versus impulsive, although in real-life, injuries entail combinations of these mechanisms. During impact loading,

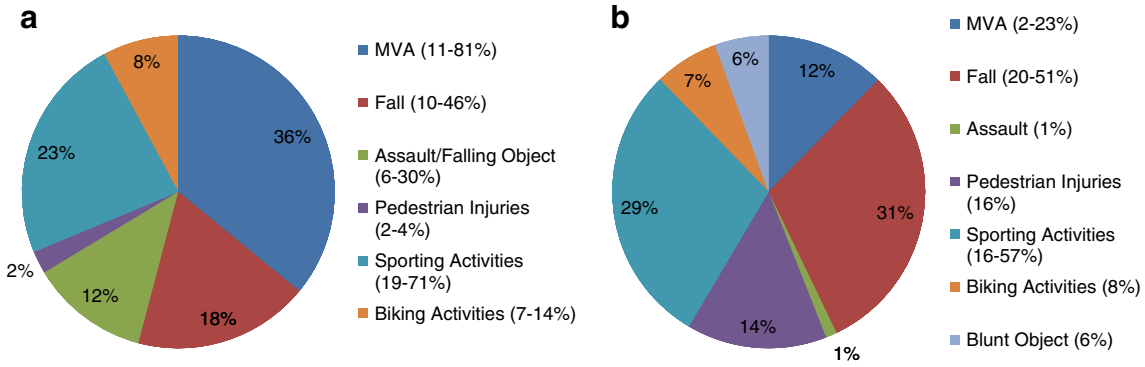

Fig. 1 Average prevalence of different mechanisms of injury in mTBI populations examined across several studies in (**a**) adults and (**b**) children. Values are adjusted to sum to 100 %, and the range for each category is indicated in the legend (Bazarian et al. 2010; Bordignon and Arruda 2002; Iverson et al. 2000; Kashluba et al. 2008b; Kraus et al. 2005; Lee et al. 2008; Lipton et al. 2009; Lundin et al. 2006; Meares et al. 2008; Thornhill et al. 2000)

the head strikes a surface, as in a fall or blow, and both contact and inertial loading takes place. In contrast, in purely impulsive head motion as in a shaken baby, the head is not hit by an object and inertial and acceleration loading occurs. In general, impact loading produces forces much greater than that produced by impulsive loading (Meaney and Smith 2011; Ommaya et al. 2002), and it is hypothesized that impact loading is more likely to result in skull fracture, brain contusion and epidural hematoma whereas inertial loading is more likely to result in injuries such as traumatic axonal injury (TAI) and subdural hematoma (Saatman et al. 2008). These variable mechanisms of injury, in combination with location and duration of injury, can result in highly unique injuries, which might cause dramatically different patterns of injury distribution and severity. Other factors can affect injury biomechanics as well, possibly mitigating the consequence of an injury. Linear and angular acceleration of the head have been shown to be reduced with the use of a helmet, although cadaveric studies have shown that the extent of brain displacement and angular speed is not significantly affected (King et al. 2011). Even as finite element modeling can describe many of these, and other possible factors involved in head injury, it still does not account for the inter-individual differences in operant parameters of a particular head injury.

Sports confer unique contexts for injury

In the United States, approximately 300,000 sports-related TBIs with reported loss of consciousness occur yearly; as only an estimated 8–19.2 % of sports-related head injuries involve loss of consciousness, the incidence of head injury is likely much higher, in the range of 1.6–3.8 million per year. Many of these injuries are in collegiate football and soccer players (Langlois et al. 2006). The myriad contextual and biomechanical variables relevant across a wide variety of sports, positions played within a sport, player skill level and available equipment sets the stage for tremendous heterogeneity of sports mTBI. In a study modeling head impacts during Olympic boxing and those seen in the National Football League, Head Injury Criterion (HIC), a measure of concussion risk, and translational acceleration were lower in Olympic boxers, whereas impact velocity was higher in Olympic boxers. While it is not possible that each sport entails exposure to a pure mechanism of injury, boxers may be subject to greater rotational forces and football players to greater translational forces, which could lead to greater risk for TAI in boxing (Viano et al. 2005). The average linear acceleration of the football player's head is generally much greater than that in hockey, with football closer to the estimated concussion threshold (Duma et al. 2005; Reed et al. 2010). Professionals might be at greater risk of concussion than amateurs as, for instance, the incidence of concussion is higher among professional boxers than amateur boxers, perhaps due to differences in safety gear or intensity of play (Moriarity et al. 2004; Viano et al. 2005).

Characteristics of play, such as player position, create additional variability in sports mTBI. Site of head impact determines the likelihood of concussion in soccer, hockey and football (Scott Delaney et al. 2006) and may be related to position played. However, not all studies agree on which impact location is most likely to result in concussion, with one study by Delaney et al. implicating the side/temporal area, and one study by Greenwald et al. implicating the top of the head (Greenwald et al. 2008; Scott Delaney et al. 2006). Using an in-helmet accelerometer system, Duma et al. demonstrated that a football player's position determines the type of impacts to which he is exposed, whether sagittal, lateral, forehead, rear helmet, or upper helmet (Duma et al. 2005). Risk for concussion and degree of rotational acceleration differ depending on player position as well as other factors such as particular play and type of game (tournament play versus regular season and play-off games) (Reed et al. 2010; Viano et al. 2007). Differences in player anthropometrics

can also lead to diverse injuries. For instance, forearm, wrist and hand anthropometry can alter the effective mass of a boxer's punch (Walilko et al. 2005).

Outcomes from sports injuries have generally been considered more favorable than those in civilian trauma (McCrea et al. 2009). For instance, sports injuries have been reported to result in shorter duration of loss of consciousness, fewer concurrent injuries, fewer financial barriers to healthcare, and more rapid recoveries (usually within 7–14 days) than those who suffer from other modes of injury resulting in mTBI (Demakis and Rimland 2010; Landre et al. 2006; McClincy et al. 2006; Williams et al. 2010). This seemingly benign natural history must be tempered by the fact that players are more likely to experience repeat-concussions and, due to under-reporting or masking of symptoms for the sake of return-to-play determinations (Grady 2010; Wall et al. 2006; Williams et al. 2010), may suffer subsequent TBI before recovery from previous injuries is complete. Thus, players are at risk for longer term decrements in neurocognitive functioning associated with repeat injury. These deficits are detectable at 3 months post-injury (Wall et al. 2006).

Factors affecting motor vehicle accident mTBI variability

Because acceleration-deceleration forces are much greater than in sports, motor vehicle accidents (MVA) may cause more severe injuries (Williams et al. 2010). PCS, especially headache and concentration difficulties, are more common after motor vehicle accidents as compared to falls, cycling and sports concussions (Bazarian and Atabaki 2001; McCauley et al. 2001; Ponsford et al. 2000), even at 1 year post-injury (Sterr et al. 2006). In terms of tissue pathology, motor vehicle accidents are more likely to result in supratentorial hematoma, DAI and brain swelling than are falls, as seen on postmortem examination (Graham et al. 1989).

Although MVA seems somewhat distinct from other types of mTBI, characteristics of a particular MVA vary greatly, leading to within group heterogeneity of pathology and outcomes. Light trucks are associated with 3.4 times higher mortality rate than passenger vehicles impacting pedestrians, when adjusted for pedestrian age and impact speed (Roudsari et al. 2004), and motorcycle accidents result in more severe head injuries than do vehicular accidents. Seatbelts can mitigate injury severity in general (Fig. 2), as the three-point belt enables the occupant to 'ride-down' with the vehicle, increasing stopping distance and thereby minimizing passenger acceleration (velocity of the individual relative to the car) (King and Yang 1995; Peterson et al. 1999). This benefit is dependent on appropriate use; 'seat belt syndrome' indicates a panel of injuries unique to children too small for appropriate seatbelt use. Airbag deployment, body position, seat location (passenger versus driver), and site of impact can all affect motor vehicle outcomes. For instance, studies have shown that when a driver's hands are positioned in front of the steering wheel, head and neck injury criteria as well as maximum linear acceleration of the head are dramatically increased (Hault-dubrulle et al. 2011). Pre-collision body posture affects excursion distance for ride-down, effectiveness of vehicular safety devices, and extent of collision between the individual and internal structures of the vehicle (Bose et al. 2010). Frontal impacts are thought to result in flexion-extension of the neck related to head motion, and side impacts are thought to translate into bending and axial rotation (Eppinger et al. 1999; Yoganandan et al. 2009). Research on rear-seat pediatric passengers shows that concussion is most common in children ages 4–12 in side or rear impact crashes (Elliott et al. 2006).

Military mTBI: the "signature wound" of modern combat

mTBI caused by improvised explosive devices (IEDs) has been described as the "signature wound of the war on terror" (Rosenfeld and Ford 2010), and typically affects male, junior rank soldiers exposed to high combat intensity, multiple blast exposures, and multiple concussions (Hoge et al.

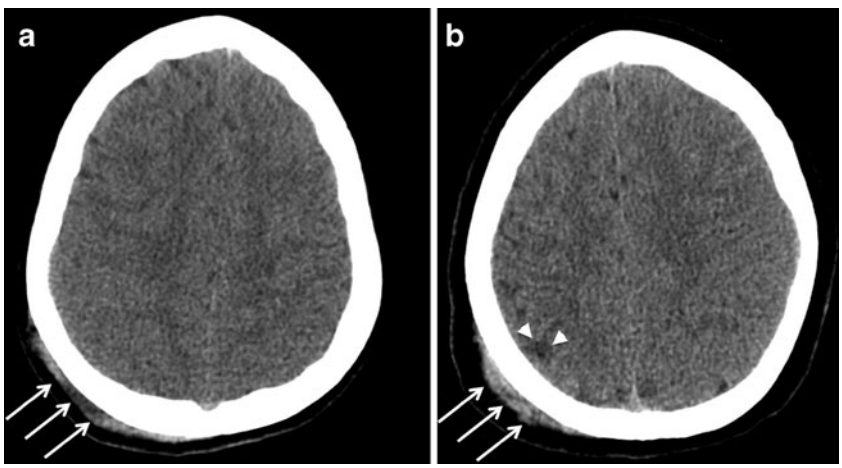

Fig. 2 Injury features alter mTBI pathology: A girl and boy, both 9, were back seat passengers during an MVA. '**a**' was restrained and sustained a scalp hematoma (*arrows*), but no visible brain abnormality. '**b**' was unrestrained and was ejected from the vehicles and sustained a bland cortical contusion visible on the CT scan (*arrowheads*)

2008; Rosenfeld and Ford 2010). Up to 20 % of American troops stationed in Iraq and Afghanistan have experienced mTBI (Belanger et al. 2009; Elder and Cristian 2009), but this may be an underestimate. Due to the prominent role of blast exposure, military mTBI may differ greatly from that occurring in the civilian population. However, it would be erroneous to consider combat blast-related mTBI as a monolithic entity. "Blast injury" may only rarely be due to the blast exposure in isolation; consequences of primary blast are not easily teased apart from those of secondary, tertiary and quaternary injures (Belanger et al. 2009; Elder and Cristian 2009). Blast injury elements include (1) positive overpressure wave, (2) underpressure wave drawing fragments leading to impact and penetrating trauma, (3) impact trauma by propelled debris and/or head impact against stationary objects and (4) burns, asphyxiation and toxic exposure (Elder and Cristian 2009; Rosenfeld and Ford 2010). These varied mechanisms in addition to other factors including type of explosive, distance from blast epicenter, use of protective gear and whether or not the blast occurred within a confined space, create both within-group differences as well as between-group heterogeneity (Rosenfeld and Ford 2010).

Mechanistic variability in combat-related mTBI is underscored by broad evidence of heterogeneity of clinical findings and adverse outcomes in this population. Chronic PCS is common (Belanger et al. 2009; Elder and Cristian 2009; Hoge et al. 2008) as are cognitive impairment and EEG abnormalities (Rosenfeld and Ford 2010). Excess adverse psychiatric outcomes, especially PTSD, as well as persistent physical health problems, are common in combat mTBI victims (Belanger et al. 2009; Hoge et al. 2008), perhaps related to combat stress and other environmental factors. At 2 years post-injury, blast victims have been shown to have higher scores on measures of PTSD than non-blast TBI patients and, on measures of learning/memory, patients with mTBI due to blast show the best performance, patients with moderate-to-severe TBI due to blast perform worst, and non-blast TBI patients show intermediate performance (Belanger et al. 2009). Terror victims, injured by explosion, gunshot, or stabbing, may also form a unique TBI subgroup as they are more likely to suffer from vascular lesions, to have abnormal CT scans, to show intracerebral hemorrhages on CT, to have longer hospital stays, and to have a significantly higher incidence of post-traumatic epilepsy than the non-terror TBI patients. Interestingly, although terror victims suffer from more severe TBI, they were more likely to return to work than non-terror victims (Schwartz et al. 2008).

Immediate effects: clinical manifestations in the acute setting

Regardless of mechanism, mTBI patients can experience anywhere from quite mild to pronounced symptoms immediately after injury. Upon initial presentation, LOC, post-traumatic amnesia (PTA) and GCS are generally used to diagnose mTBI; however, as discussed below, these three measures are not necessarily reliable prognostic indicators. The variety of type and extent of acute symptoms further emphasizes the nonuniformity of mTBI.

GCS, PTA, LOC

At the core of most definitions of mTBI is the concept of head injury associated with GCS 13–15. However, GCS score is a very poor indicator of patient status and prognosis after mTBI. Patients with GCS of 15, ostensibly the equivalent of normal consciousness, have been shown to have acute symptoms, long-term deficits, and pathology on imaging. At the same time, several studies have demonstrated that patients with GCS of 15 have better outcomes than those with GCS of 13–14, despite the fact that all three are included in a single mTBI category. For instance, the data from four cohort studies demonstrates that surgical intervention is necessary in less than 0.5 % mTBI cases with initial GCS score of 15; this statistic increases to 1 % when considering patients with GCS of 13–15 (Borg et al. 2004). A statistically significant difference in rates of positive CT findings (Fig. 3) is found in mTBI patients with different GCS scores. Patients with GCS of 13–14 have been shown to have higher incidence of initial LOC, skull fracture, pathologic CT findings, need for admission, neurological deterioration, and discharge to a rehab facility (Culotta et al. 1996; Gomez et al. 1996), and longer PTA (Tellier et al. 2009) than those with GCS of 15. Importantly, GCS does not necessarily correspond with pathoanatomic features of an injury, so that it is less useful in guiding treatment selection (Saatman et al. 2008).

In addition to GCS, LOC and PTA serve as the basis for most definitions of mTBI. Although some studies have shown that PTA (Bazarian et al. 1999; Hinton-Bayre and Geffen

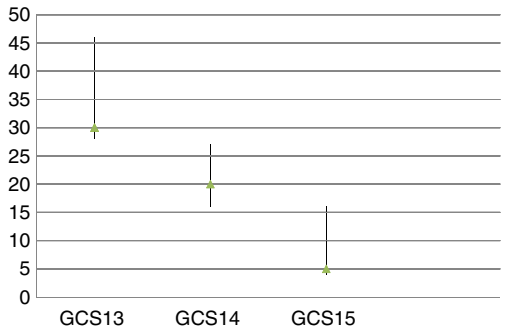

Fig. 3 Frequency (%) of CT abnormalities in mTBI patients with GCS 13–15. The x-axis indicates GCS score range and the y-axis indicates CT abnormalities (%), reported in three different studies. Each *triangle* indicates the median and the height of the *vertical line* indicates range (Borg et al. 2004; Culotta et al. 1996; Jacobs et al. 2010)

2002; Shores et al. 2008; Tellier et al. 2009) and LOC (Boran et al. 2006) are predictive of outcomes at various time points post-injury, others have shown that neither PTA (Bazarian et al. 1999; Harad and Kerstein 1992; Meares et al. 2008; Jacobs et al. 2010; Sroufe et al. 2010) nor LOC (Harad and Kerstein 1992; Hinton-Bayre and Geffen 2002; Jacobs et al. 2010; Sterr et al. 2006) are predictive of mTBI outcomes. Thus, LOC and PTA are not necessarily better prognostic indicators than GCS, and patients with similar LOC and PTA features can potentially demonstrate widely diverse outcomes. Ultimately, outcome will probably be most reliably predicted based on a complex system of clinical, pathological, and imaging variables. For instance, a cluster of seven clinical factors were found to be 100 % predictive of positive CT scan in mTBI (Haydel et al. 2000) and the presence of anxiety and noise sensitivity in the acute post-injury setting were the best predictors of post-concussive syndrome at 3 months post-injury (Dischinger et al. 2009).

Acute neurocognitive and concussive symptoms

mTBI diversity is illustrated by the panoply of acute neurocognitive and concussive symptoms found in various studies, as portrayed in Fig. 4. These results can be interpreted to represent the wide range of mTBI outcomes, produced by different injury types. It is instructive to note that, even in comparing studies employing identical tests of acute neurocognitive and concussive outcomes, reported acute outcomes for mTBI are not necessarily the same. For instance, three studies employing the Immediate Post-Concussion Assessment and Cognitive Testing battery (ImPACT) showed different degrees of impairment on the various cognitive domains (Peterson et al. 2009; Ponsford et al. 2011; Shores et al. 2008). In contrast, others have demonstrated similar findings when utilizing the same neurocognitive measures. For example, both Halterman et al. as well as van Donkelaar et al. demonstrated impaired orienting and executive, but not alerting, aspects of attention on the Attentional Network Test (ANT) in acute mTBI (Halterman et al. 2006; van Donkelaar et al. 2005). Importantly, both studies examined a population of predominantly sports-related mTBI at exactly 2 days post-injury; thus, although drawing general conclusions regarding mTBI in the acute time period, these specific findings might be relevant only to populations similar to these two groups.

Pathways to heterogeneous pathologic manifestations of MTBI: pathophysiology

Heterogeneity of mTBI pathology is likely to result from the varied interplay of myriad molecular and cellular level pathogenic mechanisms, including, either coincidentally or separately, excitotoxicity (Koura et al. 1998; Meaney and Smith 2011), inflammation (Hutchinson et al. 2007; Mellergård et al. 2011), reactive oxygen species (Cernak et al. 2001; Signoretti et al. 2010) and cerebrovascular dysfunction (Len and Neary 2011), in addition to many others. A review of these candidate mechanisms, identified and modeled in animal models of TBI, is well beyond the scope of this review (see Bigler and Maxwell 2012). However, it is notable that although numerous candidate TBI mechanisms have been identified in animal models and treatments addressing several of these mechanisms have been successful in preclinical studies, no treatment trial has yet shown efficacy in human TBI. This translational disconnect may arise from the fact that unique combinations of pathogenic mechanisms likely occur in each human TBI, dependent on host and injury factors, including the nature and spatial location (brain structure involved) of the injury.

Heterogeneous pathologic manifestations of MTBI: autopsy evidence

The heterogeneity of injuries is well-established in postmortem studies, both of TBI in general as well as a limited literature specifically addressing mTBI. Oehmichen, for example, demonstrated marked heterogeneity in TBI pathology, including the findings of red blood cells and red blood cell breakdown products, polymorphonuclear leukocytes, macrophages, fibroblasts, endothelial cells, collagenous fibers, gemistocytic and siderin-containing astrocytes, neuronophagy, axonal swelling, axonal retraction balls and mineralization of neurons within brain tissue. Multiple histopathological findings were seen at various time-points underscoring the diversity of pathology (Oehmichen et al. 2003). Even in TBI patients with similar mechanism of injury, most cases due to falls, pathologic manifestations and spatial distribution of abnormalities varied greatly between patients (Adams et al. 2001).

Autopsy studies specifically examining mTBI patients have demonstrated different sites of diffuse axonal injury, with some showing the corpus callosum as the most common site of injury (Blumbergs et al. 1995), and others showing the brainstem and lobar white matter as most common sites of diffuse axonal injury (Adams et al. 2001). In an autopsy study of a 47-year-old male with uncomplicated mTBI who died at 7 months post-injury due to unrelated causes, and who complained of symptoms at 1 month post-injury including problems with problem-solving, memory, concentration, dizziness, lack of energy, behavioral problems and anxiety, no gross abnormalities were observed, but microscopic examination revealed hemosiderin-laden macrophages in pervisacular spaces and scattered macrophages in white matter of both the frontal and temporal lobes

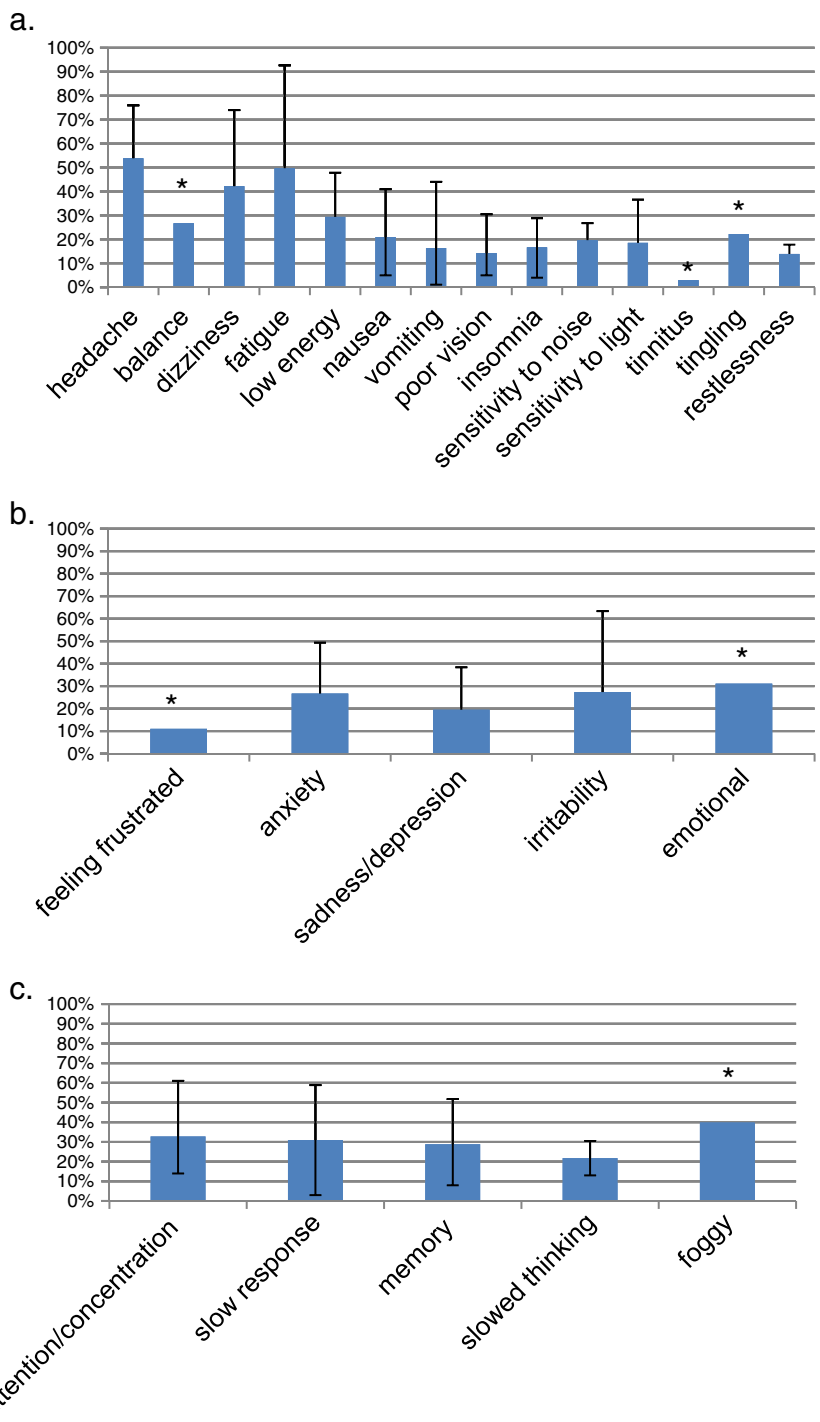

Fig. 4 Prevalence (%) of acute (**a**) somatic (**b**) emotional (**c**) cognitive symptoms at <14 days post-mTBI as based on averaged prevalence reported in several studies. *Error bars* indicate range of prevalence reported between studies; *stars* indicate that reported prevalence is based on a single study (Dischinger et al. 2009; King et al. 1995; Ponsford et al. 2011; Ayr et al. 2009)

(Bigler 2004). Very few autopsy studies have assessed blast-injury; however, two cases from WWI showed multiple punctuate hemorrhages in subcortical regions, and 9 cases from World War II showed diffuse leptomeningeal bleeding, intracerebral clots, and multifocal hemorrhages in white matter (Elder et al. 2010).

Axonal injury, assessed by staining for Amyloid Precursor Protein (APP) in mild to severe TBI post-mortem brain samples, demonstrated abnormal APP staining in all cases, from 1.75 h after injury through 28 days post-injury. The extent of APP staining was greater for those with severe head injury than those with mTBI. Patterns of APP staining varied between patients, however, with some showing randomly stained axons, some showing stained collections of parallel axons, some showing 'stress line' patterns of positively staining fibers, and some showing axonal injury

surrounding areas of hemorrhage. Interestingly, although there was a statistically significant difference in extent of APP staining between the mild and severe TBI groups, there was nevertheless an overlap between the two. For instance, a patient with GCS of 14 and LOC less than 10 min (mTBI) had an Axonal Injury Sector Score equivalent to that of a patient with GCS 3–4 (severe TBI) (Blumbergs et al. 1995). Heterogeneity of the underlying pathology belies the supposition that similar clinical manifestations indicate similar injury pathology.

Identifying MTBI pathology in vivo: imaging reveals tissue level heterogeneity

A wide range of neuroimaging findings is detectable after traumatic brain injury and the spatial distribution of these findings varies greatly. CT and magnetic resonance imaging (MRI) studies have demonstrated that a purportedly homogeneous group of patients, all with 'mild' injury, can present with normal imaging findings or a variety of abnormalities on imaging. Successive advances in imaging technology have revealed evidence of brain injury previously undetectable. This section will review evidence of pathologic heterogeneity from the imaging literature to date. However, it is likely that future advances in neuroimaging methods and practices will expose an even greater degree and variety of mTBI pathology.

Structural imaging

CT and conventional MRI findings

Most commonly, structural imaging will reveal no abnormalities in patients with clear clinical diagnoses of mTBI, in either the acute or chronic phases of injury. In fact, diagnostic criteria for mTBI may incorporate the absence of findings on structural imaging and many studies of mTBI specifically exclude patients with such abnormalities. Nonetheless, a wide variety of findings are seen in many mTBI patients. Figure 5 illustrates the total frequency, as well as specific frequency of type and location of pathology on CT and MRI in studies looking at mTBI populations. A more comprehensive review of MR imaging in mTBI is presented by Shenton et al. (2012). This section will specifically discuss the issue of intersubject variation as seen by MRI.

Many classification schemes have used the term "mild complicated TBI" to refer to patients with a clinical diagnosis of mTBI and CT/MRI abnormalities, reserving the term mTBI for those with normal imaging. This dichotomy is further discussed below. Notably, almost all of the widely known imaging indicators of TBI can be seen at any point on the injury spectrum, from mild to severe. This and the fact that gross imaging pathology does not necessarily correlate with long-term PCS and neurocognitive functioning (Niogi and Mukherjee 2010; Umile et al. 2002), underscores the variability inherent in mTBI, which might depend on pathologic features below the detection threshold of current imaging technology.

Imaging abnormalities seen in TBI may be caused by various biomechanical mechanisms. For instance, cortical contusion can result at the site of impact (coup), secondary to depressed skull fracture or merely transient deformity of the calvarium in the absence of fracture. Contusion opposite the site of impact (contrecoup) also occurs, but due to the impact of the moving brain against the often irregular skull surface (Aiken and Gean 2010; Kim and Gean 2011). Similarly, various pathologic mechanisms underpin imaging manifestations in mTBI. While excess nonspecific white matter abnormalities are seen in chronic TBI, these lesions are also seen due to many other disorders affecting white matter. The fact that, at time of injury, mTBI patients do not necessarily have greater prevalence of these lesions (Kurca et al. 2006), suggests that they develop during the subacute period due to secondary injury mechanisms. Numerous investigators have noted that the association of structural imaging findings with clinical symptoms and outcomes of mTBI is inconsistent (e.g., Niogi and Mukherjee 2010). This is true not only for total number of lesions, but also for lesion size, location, evolution over time, and type of injury seen on CT and MRI in mild as well as moderate and severe TBI (Brandstack et al. 2006; Doezema et al. 1991; Levin et al. 1987). The range of mechanistic antecedents, underlying pathologic mechanisms and clinical outcomes that may or may not be associated with well known structural indicators of TBI indicate a broad and complex range of pathology is present in the brains of mTBI patients at and after the time of injury (see Bigler and Maxwell 2012). On the other hand, an impressive relationship between neurobehavioral sequelae and location of brain lesion was seen in individual cases (Levin et al. 1987). This highlights the importance of studying structure-function relationships in individual rather than group analyses, as important findings may be masked by group analyses, due to the overwhelming heterogeneity of mTBI (see Lipton et al. 2012). Mixture-modeling and growth curve modeling are two possible alternative approaches (Yeates 2010).

The prevalence of CT findings in TBI and mTBI patients differs between subpopulations. For instance, there is an increased frequency of intracranial lesions seen on CT in mTBI patients over age 60 as compared with mTBI patients aged 14–60 (Dunham et al. 1996) and diffuse axonal injury is more common in the second and third decades of life (Cordobes et al. 1986). Among infants, non-contrast CT findings as a result of accidental head injury

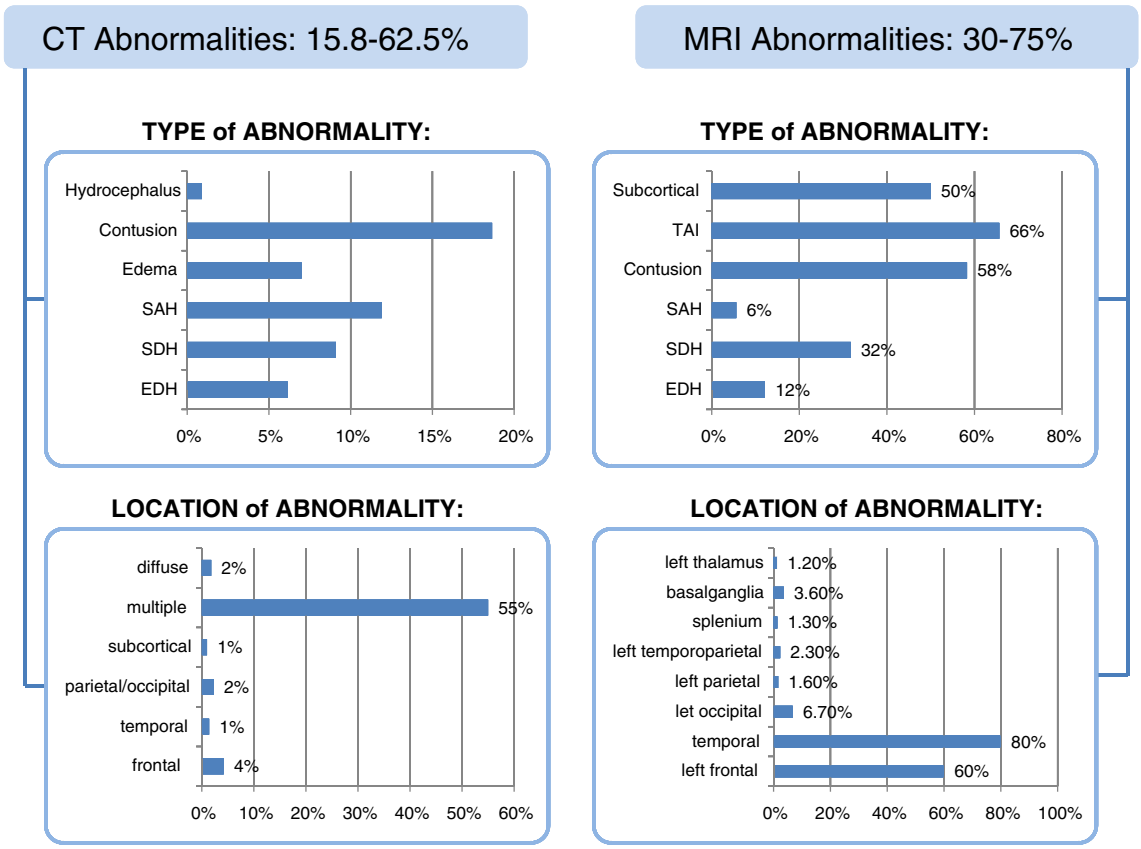

Fig. 5 Type and location of abnormalities seen on structural imaging (CT/MRI). The heterogeneity of imaging findings in mTBI (GCS 13–15, with or without PTA <30 min, with or without LOC <24 h) is demonstrated using data from selected publications (Bordignon and Arruda 2002; Iverson et al. 2000; Jacobs et al. 2010; Kurca et al. 2006; Lee et al. 2008; Styrke et al. 2007). EDH = epidural hematoma; SAH = subarachnoid hemorrhage; SDH = subdural hematoma; TAI = traumatic axonal injury

differ from those of non-accidental head injury, such that accidental injury will more likely result in homogeneous, hyperdense subdural hematomas, whereas mixed density subdural hematoma will be more common in cases of non-accidental head injury (Tung et al. 2006). CT findings might also differ with mechanism of injury, so that intracranial hemorrhage is more commonly detected in pedestrians hit by a large vehicle, followed by bicycle crashes, falls, motorcycle/moped/snowmobile crashes and contact with an object (Styrke et al. 2007). Similarly, traumatic microbleeds, indicators of TAI, are more frequently observed in TBI resulting from traffic accidents than those seen in falls and assaults (Scheid et al. 2003). Imaging abnormalities might be more common in individuals displaying certain clinical symptoms, as in one study that demonstrated headache, vomiting, increased age, alcohol or drug intoxication, anterograde amnesia, head and neck trauma, and seizures as predictive of increased likelihood of pathology on CT (McAllister et al. 2001).

Even in a highly homogeneous group of mTBI patients, structure-function relationships have not been reliably established. For instance, in a study of very mild TBI (GCS = 15, normal neurological examination, brief or no LOC, slight or no disorientation, and no changes on routine electroencephalogram), only 1/4 had MRI findings attributable to trauma. All patients in the study demonstrated poor performance on neuropsychological measures of verbal memory, and neuropsychological performance was not related to MRI findings in those patients with abnormal scans (Voller et al. 1999). Similarly, Fig. 6 shows six patients, all with GCS 15, with diverse findings on imaging exam. In a study restricted to mTBI patients with chronic symptoms, the majority due to MVA, only 25 % were found to have heterogeneous abnormalities on acute MRI. A clear relationship between symptom expression and MRI findings could not be established (Umile et al. 2002).

Complicated versus uncomplicated mTBI

The definition of mTBI developed by the Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of

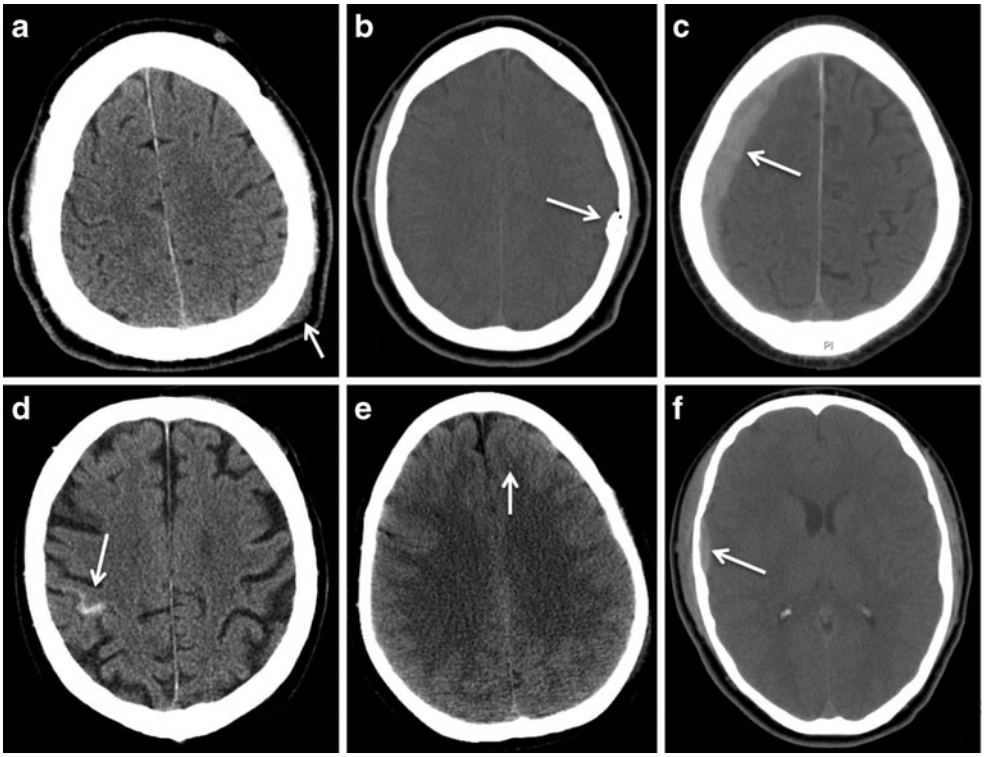

Fig. 6 Variable pathologic manifestations of mTBI: All patients presented to the ED with mTBI (GCS = 15). Imaging abnormalities varied widely despite similar clinical presentation. **a** Scalp hematoma only, with no brain abnormality. **b** Depressed skull fracture with no parenchymal brain abnormality. **c** Isolated subdural hematoma. **d** Localized subarachnoid hemorrhage. **e** Petechial hemorrhage indicative of TAI. **f** Small isolated epidural hematoma

Rehabilitation Medicine (1993) includes patients with intracranial imaging abnormalities in the mTBI category (Iverson et al. 2000). Although not all studies discussing mTBI adopt the distinction, a more recent trend in mTBI classification has been to differentiate between uncomplicated mTBI, which includes patients with GCS 13–15 not associated with MRI/CT findings, and complicated mTBI, which includes patients with GCS 13–15 associated with abnormal MRI/CT findings (Belanger et al. 2007). Complicated mTBI comprises approximately 16–21 % of all mTBI cases (Iverson et al. 2000), and is thought to result in six-month outcomes more similar to those seen in moderate traumatic brain injury (Belanger et al. 2007; Kashluba et al. 2008a; McAllister et al. 2001). For example, children with intracranial pathology detected on CT within 24 h of mTBI have been shown to have a poorer recovery at 1 year post-injury than patients with mTBI without CT abnormalities (Levin et al. 2008). mTBI patients with CT findings have also been shown to have a small but statistically significant relationship between presence of CT abnormalities and lower GCS scores, greater frequency of LOC and greater frequency of skull fractures (Iverson et al. 2000). However, even within the complicated mTBI category, studies have demonstrated that imaging findings do not necessarily predict outcome, contravening a strict structure-function relationship. Such relationships might, however, be demonstrated using other structural and functional imaging techniques.

Magnetization transfer imaging (MTI)

Studies using MTI further demonstrate the heterogeneity of mTBI and the difficulties of outcome prediction based on imaging findings, even when using a method thought to be more sensitive to edema, demyelination and Wallerian degeneration than conventional T1 and T2-weighted MRI (Belanger et al. 2007). Although regions of reduced magnetization transfer ratio (MTR) were identified in patients with poor outcomes, 50 % of patients with normal MTI also had poor long-term neurological outcomes, and one of five allegedly ‘mild’ TBI patients had MTI findings (internal capsule, white matter of temporal and occipital lobes), but only one among the five to demonstrate long-term deficits, suggesting that although deemed ‘mild,’ patients with persistent symptoms might be different from others in the same mTBI category (Bagley et al. 2000). In a study of mTBI patients with normal initial conventional MRI findings, all of whom had persistent neurocognitive symptoms at months to years after injury, decreased MTR was seen in the splenium within the patient group, but not in the pons. Still, abnormal MTI findings correlated with only 2 of 25 neurocognitive measures assessed in these patients (McGowan et al. 2000). Finally, a third study demonstrated abnormal MTI findings in five of six mTBI patients, with low MTR values not only in the splenium, but in the pons, internal capsule and temporal and occipital lobe white matter (Sinson et al. 2001). In summary, MTI studies have demonstrated that

patients with persistent symptoms might represent a different group within the mTBI designation. However, MTI does not necessarily predict neurocognitive deficits, suggesting that a further level of pathologic heterogeneity exists, inaccessible to this imaging approach.

Diffusion tensor imaging (DTI)

Because it is sensitive to changes in microstructural white matter integrity, DTI is well suited to the assessment of the white matter injury understood to be the cause of morbidity in mTBI. DTI reveals more widespread distribution of white matter abnormalities than other "structural" imaging modalities at all timepoints following mTBI and has proved sensitive, despite methodological differences between studies. Importantly, studies of DTI have revealed significant associations between abnormal white matter anisotropy and various outcome measures. While differences in findings between studies are often attributed to their methodological differences, the degree of spatial variability in abnormalities, even among similar studies, indicates intrinsic heterogeneity in the distribution of mTBI pathology. For instance, using a voxel-based analysis of uncomplicated chronic mTBI, Lipton identified areas of low FA in the corpus callosum, internal capsule, subcortical white matter, centrum semiovale and deep cerebellar white matter on both group and individual analyses (Lipton et al. 2008). In contrast, similarly employing voxel-based analysis in chronic mTBI, Rutgers showed sparing of the internal capsule (Rutgers et al. 2008) and Salmond showed involvement of the external capsule (Salmond et al. 2006). ROI analysis has evidenced DAI in uncomplicated mTBI patients at both acute and chronic time points post-injury, with decreased FA in several areas, including the splenium of the corpus callosum (Inglese et al. 2005). In contrast, ROI analysis of an mTBI population including both complicated and uncomplicated cases, Niogi et al. showed that the genu of the corpus callosum was among the most common areas of decreased FA (Niogi et al. 2008). This discrepancy highlights both the between-study heterogeneity, as well as, perhaps, the importance of studying complicated and uncomplicated mTBI as two separate entities. It is likely that variation in lesion location between studies is at least in part attributable to inter-individual differences in mTBI pathology. Each study's group-wise result will reflect the common areas affected across that unique group of patients. In the context of extensive evidence for intersubject variation in pathogenesis (previous sections) and clinical manifestations (later sections), DTI studies provide a window into the actual variation in mTBI pathology in vivo. It is essential to recognize that studies employing a priori ROIs or group-wise comparisons will be intrinsically insensitive to the component of the pathology which varies between patients. As a result, these approaches will greatly underestimate the burden of TAI likely present in the brains of individual mTBI patients.

In order to detect variability in the distribution and magnitude of mTBI pathology, studies must assess patients individually. We have developed methods for detection of regional abnormalities in anisotropy in whole brain single subject DTI datasets (Hulkower et al. 2011; Kim et al. 2011). Application of this approach to mTBI patients at multiple time points following injury reveals widespread evidence of both abnormally high and low anisotropy (Fig. 7). Areas typically considered as sites of TBI, such as the corpus callosum, are commonly affected. However, much variation is seen between subjects in the spatial distribution and magnitude of abnormal anisotropy. This approach provides a new window into the true magnitude of pathological heterogeneity, which occurs after mTBI.

Functional imaging

Functional magnetic resonance imaging (fMRI)

Study designs vary greatly across fMRI hampering comparison of results across studies, and inferences from inter-study differences regarding actual intersubject variability. Nonetheless, in an individual analysis, areas of activation showed a wide pattern of distribution, and differed between each subject tested (Chen et al. 2004). This could reflect inter-individual variability of brain activity, not detected by CT or MRI and even neurocognitive testing, which is due to either actual injury or the development of compensatory networks. When employing the same task paradigm, fMRI studies have shown differing results; as in a comparison between studies by Chen and Gosselin, both of which employed an externally ordered task to mobilize working memory in mTBI patients. While both demonstrated decreased activation in the parietal and frontal regions, only Gosselin identified decreased activation in the thalamus (Chen et al. 2004; Gosselin et al. 2011). Although Gosselin did not demonstrate a significant relationship between working memory function and areas of decreased activation, a negative correlation was established between areas of activation and PCS (Gosselin et al. 2011). While these differences may at least in part be due to study variables (hardware, software, MRI acquisition parameters, etc.) they provide some indication of the complicated relationship which exists among various mTBI outcomes and brain changes (see, for instance, Mayer, et al. and Stevens et al. 2012). Separation of neurocognitive outcomes from PCS might represent a false distinction.

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT)

PET and SPECT provide physiological information, glucose metabolism and cerebral perfusion, respectively, not available

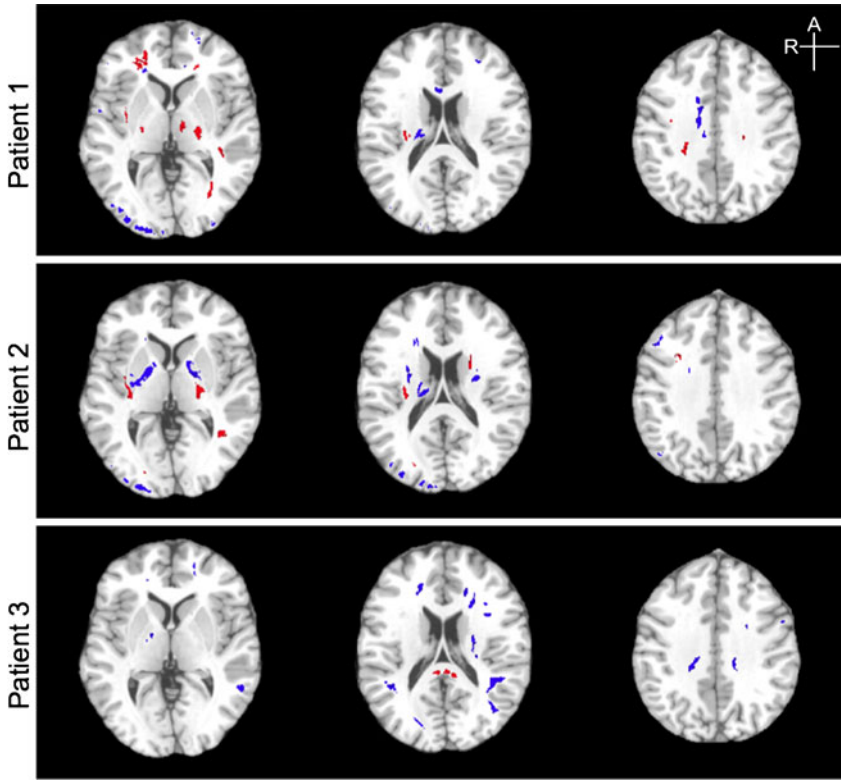

Fig. 7 Variability of TAI in mTBI: Individualized voxelwise assessment of fractional anisotropy images ($p<0.01$; comparison to 40 normals) from DTI in 3 individual mTBI patients (GCS = 15) reveals areas of abnormally low (*red*) and abnormally high (*blue*) FA in each individual, but the spatial distribution of abnormalities varies greatly among individuals. Structural MR images were entirely normal in these individuals

from structural studies and might thus be expected to reveal a new aspect of inter-individual variation than previously shown. PET shows areas of both increased and decreased metabolic activity across a wide range of brain regions in mTBI patients. For instance, in one study, all patients showed at least one area of abnormality and the valence of the effect (high or low metabolism) varied between patients at a given brain location. Moreover, patients with similar symptoms did not necessarily demonstrate abnormalities in the same locations (Gross et al. 1996). In contrast, in a group analysis, Humayan found similarities between patients with similar persistent symptoms (Humayun et al. 1989). SPECT studies reveal variable regional perfusion abnormalities which correlate with outcome measures to differing degrees between studies and patients (Abdel-Dayem et al. 1998; Ichise et al. 1994; Kant et al. 1997; Nedd et al. 1993; Umile et al. 2002).

Electrophysiology

Electroencephalography (EEG) and magnetoencephalography (MEG) studies are important because they directly measure, albeit at relatively crude spatial resolution, actual neuronal activity, whereas functional imaging measures (functional magnetic resonance imaging (fMRI), PET, SPECT) detect function indirectly. EEG detects abnormalities that are not necessarily concordant with CT, MRI or SPECT (Kant et al. 1997). As seen in fMRI studies, although task performance may not differ from controls, electrophysiological abnormalities are detectable in mTBI. For instance, significant attenuation of sustained posterior contralateral negativity waveform amplitude was related to number of sports concussions, despite normal working memory function (Theriault et al. 2011) and the expected N350 peak was not detected in mTBI patients performing a working memory task (Gosselin et al. 2011). Similarly, Montgomery demonstrated abnormalities of brainstem function, which differed greatly across mTBI patients (Montgomery et al. 1991). Thus, EEG studies reveal additional aspects of abnormal brain function in mTBI. Correlation of electrophysiological studies with imaging findings is likely to be a fruitful path toward refining our understanding of the breadth of structure-function disturbances in mTBI and will likely further expose and characterize inter-subject variation. Proof of principle in this area has been accomplished, as in the elegant study correlating regional white matter abnormalities detected with DTI and abnormal slow wave MEG findings in individual military mTBI patients (Huang et al. 2009).

The endpoint: heterogeneity of functional outcomes in mTBI

Functional outcomes after mTBI are extremely diverse. At the most basic level, despite similar injuries, approximately 70 % of patients will experience full recovery after mTBI whereas 30 %, the "miserable minority," will suffer long-term symptoms and impairment (Alexander 1995), which in

turn will vary from mild and annoying to frankly disabling. This consistently observed finding, despite study differences, results from the varied interaction of patient and injury related variables, which generate unique patterns of mTBI pathology.

PCS and neurocognitive outcomes

PCS include several somatic (e.g., headache/fatigue), cognitive (e.g., inattention, forgetfulness, slowed processing), or affective symptoms (e.g., irritability, disinhibition) seen in the aftermath of head injury (Yeates 2010). While some prior studies have reported that the long-term effects of mTBI on neurocognitive function (Binder et al. 1997; Frencham et al. 2005; Schretlen and Shapiro 2003) and post-concussive syndrome (Belanger et al. 2005) are minimal and likely resolve within 3 months, numerous studies report that 15–47 % of mTBI cases result in persistent symptoms and deficits (e.g., Konrad et al. 2010; Ponsford et al. 2000; Thornhill et al. 2000). Although it has become clear that a subset of mTBI patients will suffer persistent symptoms, the nature of symptoms and deficits varies widely across patients, even when different patient groups are assessed with the same outcome measures for neurocognitive function (e.g., Konrad et al. 2010; Leininger et al. 1990; Ponsford et al. 2000) or PCS (King et al. 1995; Lundin et al. 2006). Vanderploeg presents evidence that detection of neurocognitive impairment in mTBI might require individualized testing strategies, since individual injuries disrupt different specialized neural networks (Vanderploeg et al. 2005). These findings likely reflect diversity of both pathology and host compensation for injury (e.g., compensatory plasticity). Figure 8 shows the prevalence of PCS and neurocognitive deficits across mTBI patients, and Fig. 9 shows the prevalence of somatic, emotional and cognitive PCS. It must be understood, however, that the varied occurrence of different clinical manifestations will not be uniform across mTBI patients, further expanding inter-subject variation.

Psychiatric disease following mTBI

The diversity of psychiatric diagnoses seen in the wake of mTBI (e.g., depression, generalized anxiety disorder, adjustment disorder, psychotic disorders and substance abuse/dependence and, in children, ADHD) further underscores clinical heterogeneity across this population (Fann et al. 2004; Mooney and Speed 2001). Although the existence of premorbid psychiatric symptoms or frank psychopathology prior to mTBI may be a factor contributing to its variable prevalence after mTBI, it is important to recognize this as a manifestation of pre-injury variability which is likely to be a large factor in the ultimate heterogeneity of mTBI pathology and outcomes (see The **Substrate** above). Thus, the heterogeneous incidence of psychiatric disease after mTBI is likely a manifestation of variation in brain pathology and post-injury compensatory responses. Figure 8 displays the prevalence of psychiatric diagnoses after mTBI.

PTSD and mTBI

Anterior frontal and temporal regions are implicated in the pathogenesis of PTSD (Elder and Cristian 2009). Because these regions are common sites of brain injury, PTSD is not an unexpected outcome after mTBI and is, in fact, commonly reported (Bryant et al. 2009; Carlson et al. 2011; Hajek et al. 2010). An intriguing explanation of the strong association between mTBI and PTSD is the relatively short duration of PTA in patients with

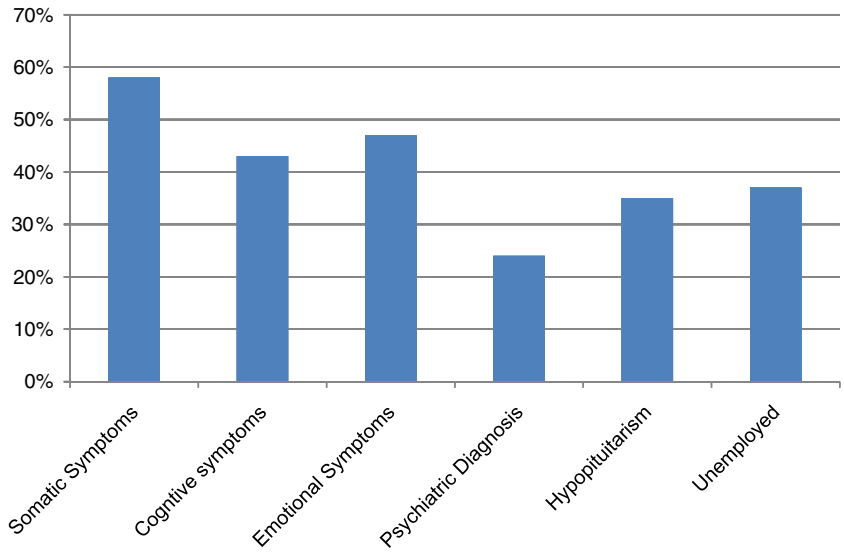

Fig. 8 Prevalence (%) of post-concussive symptoms >3 months post-mTBI (Aimaretti et al. 2005; Doctor et al. 2005; Fann et al. 2004; Friedland and Dawson 2001; Rimel et al. 1981; Schneider et al. 2007; Stambrook et al. 1990; Tanriverdi et al. 2007; Thornhill et al. 2000)

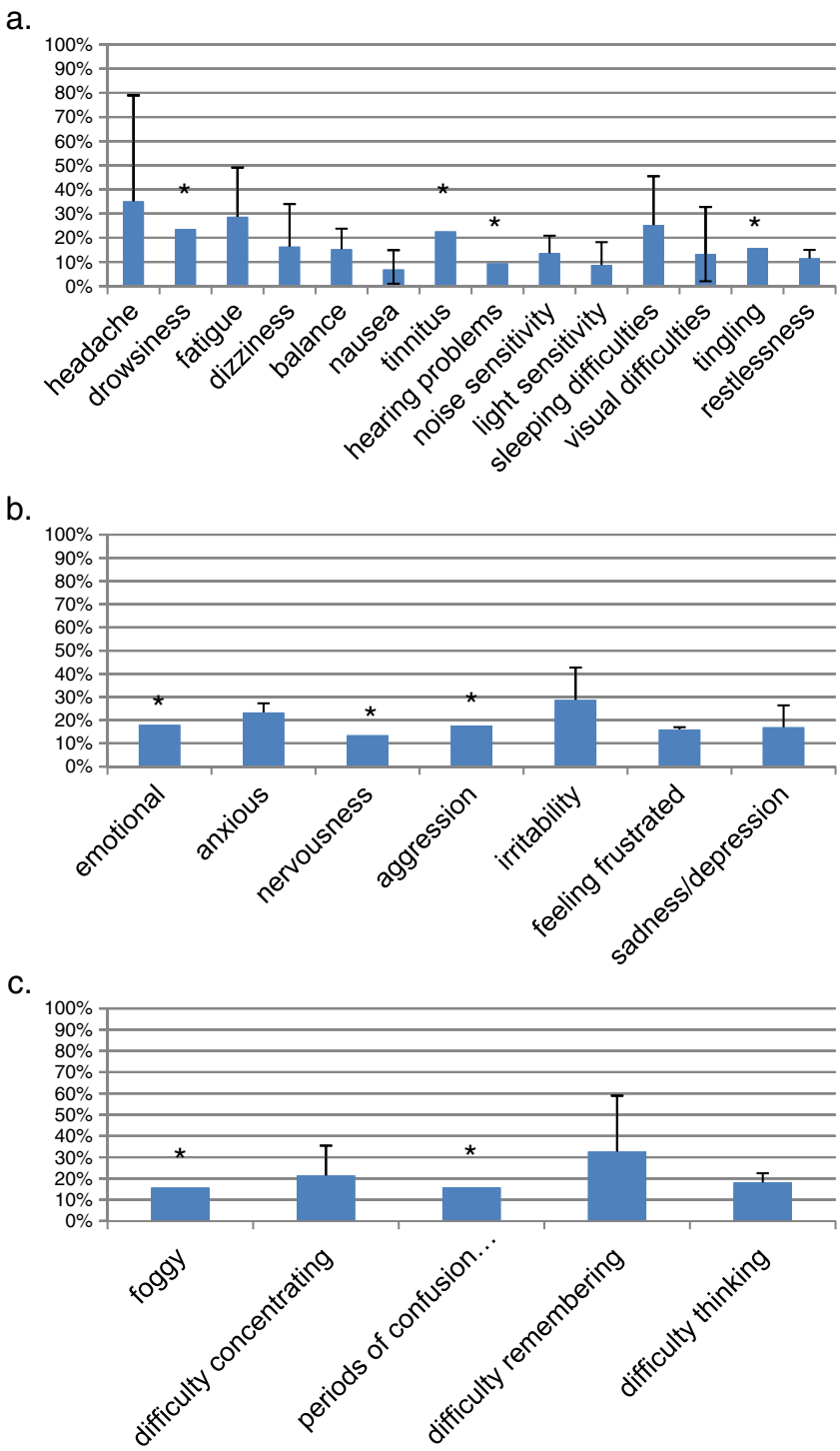

Fig. 9 Prevalence (%) of chronic (**a**) somatic (**b**) emotional and (**c**) cognitive symptoms at >3 months post-mTBI based on averaged prevalence reported in several studies. *Error bars* indicate the range of prevalence across studies; stars indicate that prevalence is based on a single study (Dischinger et al. 2009; Fann et al. 2004; King et al. 1995; Kraus et al. 2005; Lundin et al. 2006; Mooney and Speed 2001; Ponsford et al. 2011; Rimel et al. 1981)

mild degrees of injury. This may facilitate recall of the traumatic event and formation of pathological memory, which is thought to be essential to the pathogenesis of PTSD. However, it remains unclear whether mTBI patients actually suffer PTSD per se, or simply endorse PTSD-like symptoms directly related to brain injury (Belanger et al. 2009). This may, however, be a simply semantic distinction.

Endocrine

The pituitary is vulnerable to head injury because it is immobilized within the sella turcica and the infundibulum is suspended under some tension between the pituitary and hypothalamus (Kelly et al. 2006 clin 162). Disruption of the hypothalamic-pituitary axis has been shown to result in pituitary dysfunction after mTBI, including repeated concussion

in adult boxers (Kelestimur 2005; Tanriverdi et al. 2007, 2010) and adolescent soccer players (Ives et al. 2007). Varied endocrine consequences may include diabetes insipidus (Chou et al. 2009), hypothyroidism, arrested puberty, secondary amenorrhea, and reduced libido (Acerini et al. 2006; Tanriverdi et al. 2010). A meta-analysis demonstrated the pooled prevalence of hypopituitarism following mTBI to be 16.8 % (10.9 %–25.0 %) (Schneider et al. 2007) (Fig. 8). More than half of mTBI patients have at least one anterior pituitary hormone deficiency, most commonly growth hormone (GH) deficiency (Aimaretti et al. 2005; Tanriverdi et al. 2007). Post-injury pituitary dysfunction, especially of GH, impacts neurobehavioral function and can contribute to the heterogeneity of mTBI outcomes (Kelly et al. 2006).

Other manifestations of mTBI: visual and auditory dysfunction and seizures

While less commonly recognized, mTBI patients have increased oculomotor latency and error during target tasks, which may be due to brainstem injury and cause visual symptoms (Suh et al. 2006). Tinnitus, hyperacusis and hearing loss have been objectively demonstrated after mTBI (Nolle et al. 2004) and the basilar membrane of the cochlea, the tympanic membrane, and the ossicular chain are injured at relatively low blast pressures (Patterson and Hamernik 1997); in fact, 35.2 % of soldiers with blast induced concussion have tympanic membrane perforation (Xydakis et al. 2007). mTBI patients are also at increased risk for post-traumatic epilepsy. Relative risk of seizures in children after mTBI is 2.2, and this risk increases with age (Christensen et al. 2009). The visual and seizure disorders represent additional manifestations of brain injury, which, as they occur variably across patients, add to variation of pathological and clinical manifestations of mTBI. In addition, however, these aspects of injury as well as auditory disturbances, which may be a result of peripheral injury, may greatly alter sensory input and cognition in the aftermath of mTBI, further complicating recovery and adding additional heterogeneity to the final post-injury state.

Discussion: embracing the chaos that is in mTBI

Scope of the problem and the opportunities it presents

This review has presented the scope and context of inter-subject variation in mTBI, from pre-injury factors to injury mechanisms, pathology and clinical manifestations. While the scope of clinical heterogeneity of mTBI has long been evident, only recently have advanced neuroimaging techniques given us a broad window into the degree of pathologic heterogeneity of the disorder. Recent medical advances, such as genomically guided interventions in cancer, have embraced the notion of patient specific disease, which will be best treated using personalized medicine approaches. We propose that "embracing the chaos," the patient-to-patient variations in mechanisms, pathology and clinical manifestations that are inherent in mTBI, will prove a fruitful path to improved research and clinical outcomes.

Advancing clinical care in mTBI

At present, functional assessments and imaging techniques can identify findings related to mTBI. These determinations have clinical utility, as they may provide some reassurance as to the presence of brain injury in symptomatic patients, but it is likely that current approaches have limited sensitivity. Importantly, it remains unclear how long-term outcomes can be reliably predicted in clinical practice. Refining our approach to TBI diagnosis, in light of inter-individual differences, can facilitate the development of effective prognostic tools and algorithms. These approaches will immediately benefit clinical care by permitting judicious use of assessment techniques and appropriate allocation of resources for follow-up and treatment. Patients can thus benefit, without needlessly burdening themselves, their healthcare providers and the healthcare system.

Jumpstarting research into treatment of mTBI

The failure of multiple clinical trials of TBI therapy, despite efficacy in preclinical models, is potentially due, at least in part, to inappropriate patient classification [we note here that classification may be affected by true inter-subject differences as well as apparent differences created by choice of assessment tool] and reductionist model systems. No two head injuries can be identical and, perhaps, they are only occasionally similar enough to respond to the same therapeutic intervention. Approaches that do not account for the inter-individual variation in pathology and patient characteristics that pertain to real-life clinical trial participants, may entirely miss therapeutic targets. For example, group analyses typically employed in research studies, which have been used to classify and categorize TBI, might relegate distinct pathological entities, with distinct treatment requirements, to the realm of statistical outliers (Pertab et al. 2009; Taylor et al. 2010). Simplification and reductionism is valuable in basic science investigation. However, translational research, which will actually improve patient outcomes, must embrace the complexity of human mTBI in its choice and development of preclinical model systems. Animal, cadaveric and synthetic (dummy) models cannot reproduce each and every, or perhaps any, mTBI scenario or account for individual differences in age, gender and anthropometrics (Drew and Drew 2004; Sabet et al. 2008; Viano et al. 2007)

(see empirical paper by Lipton et al. (2012), which discusses the application of a voxel-wise Z-map approach to the study of DTI in individual mTBI subjects). Furthermore, model systems may not be as straightforward and reproducible as intended; linear acceleration models, for example, can produce angular acceleration in the brain because vascular, neural and dural structures serve as axes about which the brain can rotate (Bayly et al. 2005). Better model systems are clearly needed, which embrace and address the complexity of real-life TBI.

Recent workshops have addressed lack of progress in TBI research, which ultimately restrains advances in clinical care (Saatman et al. 2008; Zitnay et al. 2008). New paradigms, which embrace heterogeneity of mTBI, in both preclinical and clinical investigation as well the appreciation of this variability in clinical care, can offer much promise for enhancing outcomes and mitigating the burden of mTBI on its victims.

Summary Points

- **mTBI is highly heterogeneous:** Despite classification schemes, mTBI is not a single clinical or pathologic entity.
- **Each individual is unique:** Inter-individual pre-morbid differences provide a varied substrate, which will respond differently to the same injury mechanism.
- **Each injury is unique:** Context (i.e., sport injury, motor vehicle accident, military injury) and biomechanics (e.g., angular acceleration, linear acceleration, location and duration of impact) provide a mechanistic basis for varied injury location and severity across the brain of each mTBI patient.
- **Many mechanisms are involved:** The relative contribution of varied cellular and molecular mechanisms, in combination with patient characteristics will uniquely confer the final pathologic and clinical endpoint.
- **Imaging reveals pathologic heterogeneity:** Most mTBI patients show no abnormalities on conventional imaging; when findings are present, they predict outcomes poorly. Newer imaging techniques, particularly diffusion MRI, reveal more and more varied brain abnormalities in mTBI.
- **Diverse outcomes:** Variability in the range and severity of functional outcomes in mTBI patients implicates the unique interaction between patient and injury characteristics in each individual.
- **Personalizing mTBI research:** Reductionist models, although important, are inherently flawed in that they do not represent the full scope of mTBI, both in terms of substrate as well as injury mechanism, and can therefore never truly address the real-life mTBI clinical problem. Personalized medicine approaches are required.
- **Promise for the future:** Understanding and embracing the great variety of mechanistic, pathologic and clinical manifestations of mTBI can improve research efficacy and clinical care of patients.

Disclosure The authors declare that they have no conflicts of interest

References

Abdel-Dayem, H. M., Abu-Judeh, H., Kumar, M., Atay, S., Naddaf, S., El-Zeftawy, H., et al. (1998). SPECT brain perfusion abnormalities in mild or moderate traumatic brain injury. *Clinical Nuclear Medicine, 23*(5), 309–317.

Acerini, C. L., Tasker, R. C., Bellone, S., Bona, G., Thompson, C. J., & Savage, M. O. (2006). Hypopituitarism in childhood and adolescence following traumatic brain injury: The case for prospective endocrine investigation. *European Journal of Endocrinology/European Federation of Endocrine Societies, 155*(5), 663–669. doi:10.1530/eje.1.02284.

Adams, J. H., Graham, D., & Jennett, B. (2001). The structural basis of moderate disability after traumatic brain damage. *Journal of Neurology, Neurosurgery, and Psychiatry, 71*(4), 521.

Aiken, A. H., & Gean, A. D. (2010). Imaging of head trauma. In *vol. 45* (pp. 63–79). Elsevier Ltd.

Aimaretti, G., Ambrosio, M. R., Di Somma, C., Gasperi, M., Cannavo, S., Scaroni, C., et al. (2005). Residual pituitary function after brain injury-induced hypopituitarism: A prospective 12-month study. *Journal of Clinical Endocrinology and Metabolism, 90* (11), 6085–6092. doi:10.1210/jc.2005-0504.

Alexander, M. P. (1995). Mild traumatic brain injury: pathophysiology, natural history, and clinical management. *Neurology.*

Allen, D. N., Goldstein, G., Caponigro, J. M., & Donohue, B. (2009). The effects of alcoholism comorbidity on neurocognitive function following traumatic brain injury. *Applied Neuropsychology, 16*(3), 186–192. doi:10.1080/09084280903098687.

Alterman, A. I., & Tarter, R. E. (1985). Relationship between familial alcoholism and head injury. *Journal of Studies on Alcohol, 46*(3), 256–258.

Ariza, M., Pueyo, R., Matarin Mdel, M., Junque, C., Mataro, M., Clemente, I., et al. (2006). Influence of APOE polymorphism on cognitive and behavioural outcome in moderate and severe traumatic brain injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 77*(10), 1191–1193. doi:10.1136/jnnp.2005.085167.

Ayr, L. K., Yeates, K. O., Taylor, H. G., & Browne, M. (2009). Dimensions of postconcussive symptoms in children with mild traumatic brain injuries. *Journal of the International Neuropsychological Society, 15*(1), 19–30. doi:10.1017/s1355617708090188.

Bagley, L. J., McGowan, J. C., Grossman, R. I., Sinson, G., Kotapka, M., Lexa, F. J., et al. (2000). Magnetization transfer imaging of traumatic brain injury. *Journal of Magnetic Resonance Imaging, 11*(1), 1–8.

Barlow, K. M., Crawford, S., Stevenson, A., Sandhu, S. S., Belanger, F., & Dewey, D. (2010). Epidemiology of postconcussion syndrome in pediatric mild traumatic brain injury. *Pediatrics, 126*(2), e374–e381. doi:10.1542/peds.2009-0925.

Baugh, C. M., Stamm, J. M., Riley, D. O., Gavett, B. E., Shenton, M. E., Lin, A. P., et al. (2012). Chronic traumatic encephalopathy: neurodegeneration following repetitive concussive and subconcussive brain trauma. *Brain Imaging and Behavior.* This special issue.

Bayly, P. V., Cohen, T. S., Leister, E. P., Ajo, D., Leuthardt, E. C., & Genin, G. M. (2005). Deformation of the human brain induced by mild acceleration. *Journal of Neurotrauma, 22*(8), 845–856. doi:10.1089/neu.2005.22.845.

Bazarian, J. J., & Atabaki, S. (2001). Predicting postconcussion syndrome after minor traumatic brain injury. *Academic Emergency Medicine, 8*(8), 788–795.

Bazarian, J. J., Wong, T., Harris, M., Leahey, N., Mookerjee, S., & Dombovy, M. (1999). Epidemiology and predictors of postconcussive syndrome after minor head injury in an emergency population. *Brain Injury, 13*(3), 173–189.

Bazarian, J. J., Pope, C., McClung, J., Cheng, Y. T., & Flesher, W. (2003). Ethnic and racial disparities in emergency department care for mild traumatic brain injury. *Academic Emergency Medicine, 10*(11), 1209–1217.

Bazarian, J. J., McClung, J., Shah, M. N., Cheng, Y. T., Flesher, W., & Kraus, J. (2005). Mild traumatic brain injury in the United States, 1998–2000. *Brain Injury, 19*(2), 85–91.

Bazarian, J. J., Blyth, B., Mookerjee, S., He, H., & McDermott, M. P. (2010). Sex differences in outcome after mild traumatic brain injury. *Journal of Neurotrauma, 27*(3), 527–539. doi:10.1089/neu.2009.1068.

Belanger, H. G., Curtiss, G., Demery, J. A., Lebowitz, B. K., & Vanderploeg, R. D. (2005). Factors moderating neuropsychological outcomes following mild traumatic brain injury: A meta-analysis. *Journal of the International Neuropsychological Society, 11*(3), 215–227. doi:10.1017/s1355617705050277.

Belanger, H. G., Vanderploeg, R. D., Curtiss, G., & Warden, D. L. (2007). Recent neuroimaging techniques in mild traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 19*(1), 5–20. doi:10.1176/appi.neuropsych.19.1.5.

Belanger, H. G., Kretzmer, T., Yoash-Gantz, R., Pickett, T., & Tupler, L. A. (2009). Cognitive sequelae of blast-related versus other mechanisms of brain trauma. *Journal of the International Neuropsychological Society, 15*(1), 1–8. doi:10.1017/s1355617708090036.

Bigler, E. D. (2004). Neuropsychological results and neuropathological findings at autopsy in a case of mild traumatic brain injury. *Journal of the International Neuropsychological Society, 10*(5), 794–806. doi:10.1017/s1355617704105146.

Bigler, E. D., & Maxwell, W. L. (2011). Neuroimaging and neuropathology of TBI. *NeuroRehabilitation, 28*(2), 63–74. doi:10.3233/nre-2011-0633.

Bigler, E. D., & Maxwell, W. L. (2012). Neuropathology of mild traumatic brain injury: relationship to neuroimaging findings. *Brain Imaging and Behavior*. This special issue.

Binder, L. M., Villanueva, M. R., Howieson, D., & Moore, R. T. (1993). The Rey AVLT recognition memory task measures motivational impairment after mild head trauma* 1. *Archives of Clinical Neuropsychology, 8*(2), 137–147.

Binder, L. M., Rohling, M. L., & Larrabee, G. J. (1997). A review of mild head trauma. Part I: Meta-analytic review of neuropsychological studies. *Journal of Clinical and Experimental Neuropsychology, 19*(3), 421–431. doi:10.1080/01688639708403870.

Blinman, T. A., Houseknecht, E., Snyder, C., Wiebe, D. J., & Nance, M. L. (2009). Postconcussive symptoms in hospitalized pediatric patients after mild traumatic brain injury. *Journal of Pediatric Surgery, 44*(6), 1223–1228. doi:10.1016/j.jpedsurg.2009.02.027.

Blumbergs, P. C., Scott, G., Vis, J. I. M. M., Wainwright, H., Simpson, D. A., & McLean, A. J. (1995). Topography of axonal injury as defined by amyloid precursor protein and the sector scoring method in mild and severe closed head injury. *Journal of Neurotrauma, 12*(4), 565–572.

Bohnen, N., Zutphen, W. V., Twijnstra, A., Wijnen, G., Bongers, J., & Jolles, J. (1994). Late outcome of mild head injury: Results from a controlled postal survey. *Brain Injury, 8*(8), 701–708.

Boran, B. O., Boran, P., Barut, N., Akgun, C., Celikoglu, E., & Bozbuga, M. (2006). Evaluation of mild head injury in a pediatric population. *Pediatric Neurosurgery, 42*(4), 203–207. doi:10.1159/000092355.

Bordignon, K. C., & Arruda, W. O. (2002). CT scan findings in mild head trauma: A series of 2,000 patients. *Arquivos de Neuro-Psiquiatria, 60*(2-A), 204–210.

Borg, J., Holm, L., Cassidy, J. D., Peloso, P., Carroll, L., von Holst, H., et al. (2004). Diagnostic procedures in mild traumatic brain injury: Results of the WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of Rehabilitation Medicine, 36* (Supplement 43), 61–75.

Bose, D., Crandall, J., Untaroiu, C., & Maslen, E. (2010). Influence of pre-collision occupant parameters on injury outcome in a frontal collision. *Accident Analysis and Prevention, 42*(4), 1398–1407.

Brandstack, N., Kurki, T., Tenovuo, O., & Isoniemi, H. (2006). MR imaging of head trauma: Visibility of contusions and other intraparenchymal injuries in early and late stage. *Brain Injury, 20*(4), 409–416. doi:10.1080/02699050500487951.

Bryant, R. A., Creamer, M., O'Donnell, M., Silove, D., Clark, C. R., & McFarlane, A. C. (2009). Post-traumatic amnesia and the nature of post-traumatic stress disorder after mild traumatic brain injury. *Journal of the International Neuropsychological Society, 15*(6), 862–867.

Carlson, K. F., Kehle, S. M., Meis, L. A., Greer, N., Macdonald, R., Rutks, I., et al. (2011). Prevalence, assessment, and treatment of mild traumatic brain injury and posttraumatic stress disorder: A systematic review of the evidence. *The Journal of Head Trauma Rehabilitation, 26*(2), 103–115. doi:10.1097/HTR.0b013e3181e50ef1.

Carroll, L., Cassidy, J. D., Holm, L., Kraus, J., & Coronado, V. (2004). Methodological issues and research recommendations for mild traumatic brain injury: The WHO Collaborating Centre Task Force on Mild Traumatic Brain Injury. *Journal of Rehabilitation Medicine, 36*(Supplement 43), 113–125.

Cernak, I., Wang, Z., Jiang, J., Bian, X., & Savic, J. (2001). Ultrastructural and functional characteristics of blast injury-induced neurotrauma. *The Journal of Trauma, 50*(4), 695–706.

Chamelian, L., Reis, M., & Feinstein, A. (2004). Six-month recovery from mild to moderate traumatic brain injury: The role of APOE-epsilon4 allele. *Brain, 127*(Pt 12), 2621–2628. doi:10.1093/brain/awh296.

Chen, J. K., Johnston, K. M., Frey, S., Petrides, M., Worsley, K., & Ptito, A. (2004). Functional abnormalities in symptomatic concussed athletes: An fMRI study. *NeuroImage, 22*(1), 68–82. doi:10.1016/j.neuroimage.2003.12.032.

Chou, Y. C., Wang, T. Y., Yang, P. Y., Meng, N. H., & Chou, L. W. (2009). Permanent central diabetes insipidus after mild traumatic brain injury. *Brain Injury, 23*(13–14), 1095–1098. doi:10.3109/02699050903379396.

Christensen, J., Pedersen, M. G., Pedersen, C. B., Sidenius, P., Olsen, J., & Vestergaard, M. (2009). Long-term risk of epilepsy after traumatic brain injury in children and young adults: A population-based cohort study. *Lancet, 373*(9669), 1105–1110. doi:10.1016/s0140-6736(09)60214-2.

Cicerone, K. D., & Kalmar, K. (1997). Does premorbid depression influence post-concussive symptoms and neuropsychological functioning? *Brain Injury, 11*(9), 643–648.

Collins, M. W., Grindel, S. H., Lovell, M. R., Dede, D. E., Moser, D. J., Phalin, B. R., et al. (1999). Relationship between concussion and neuropsychological performance in college football players. *JAMA: The Journal of the American Medical Association, 282* (10), 964–970.

Collins, M. W., Lovell, M. R., Iverson, G. L., Cantu, R. C., Maroon, J. C., & Field, M. (2002). Cumulative effects of concussion in high school athletes. *Neurosurgery, 51*(5), 1175–1179. discussion 1180–1171.

Cordobes, F., Lobato, R. D., Rivas, J. J., Cabrera, A., Sarabia, M., Castro, S., et al. (1986). Post-traumatic diffuse axonal brain injury. Analysis of 78 patients studied with computed tomography. *Acta Neurochirurgica, 81*(1–2), 27–35.

Corrigan, J. D. (1995). Substance abuse as a mediating factor in outcome from traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 76*(4), 302–309.

Covassin, T., Swanik, C. B., Sachs, M., Kendrick, Z., Schatz, P., Zillmer, E., et al. (2006). Sex differences in baseline neuropsychological function and concussion symptoms of collegiate athletes. *British Journal of Sports Medicine, 40*(11), 923–927. doi:10.1136/bjsm.2006.029496. discussion 927.

Covassin, T., Stearne, D., & Elbin, R. (2008). Concussion history and postconcussion neurocognitive performance and symptoms in collegiate athletes. *Journal of Athletic Training, 43*(2), 119–124. doi:10.4085/1062-6050-43.2.119.

Culotta, V. P., Sementilli, M. E., Gerold, K., & Watts, C. C. (1996). Clinicopathological heterogeneity in the classification of mild head injury. *Neurosurgery, 38*(2), 245–250.

De Guise, E., Leblanc, J., Dagher, J., Lamoureux, J., Jishi, A. A., Maleki, M., et al. (2009). Early outcome in patients with traumatic brain injury, pre-injury alcohol abuse and intoxication at time of injury. *Brain Injury, 23*(11), 853–865. doi:10.1080/02699050903283221.

De Silva, M. J., Roberts, I., Perel, P., Edwards, P., Kenward, M. G., Fernandes, J., et al. (2009). Patient outcome after traumatic brain injury in high-, middle- and low-income countries: Analysis of data on 8,927 patients in 46 countries. *International Journal of Epidemiology, 38*(2), 452–458. doi:10.1093/ije/dyn189.

Demakis, G. J., & Rimland, C. A. (2010). Untreated mild traumatic brain injury in a young adult population. *Archives of Clinical Neuropsychology, 25*(3), 191–196. doi:10.1093/arclin/acq004.

Derosia, J., Yoganandan, N., & Frank, A. P. (2004). Rear impact responses of different sized adult Hybrid III dummies. *Traffic Injury Prevention, 5*(1), 50–55.

Dick, R. W. (2009). Is there a gender difference in concussion incidence and outcomes? *British Journal of Sports Medicine, 43* (Suppl 1), i46–i50. doi:10.1136/bjsm.2009.058172.

Dischinger, P. C., Ryb, G. E., Kufera, J. A., & Auman, K. M. (2009). Early predictors of postconcussive syndrome in a population of trauma patients with mild traumatic brain injury. *The Journal of Trauma, 66*(2), 289–296. doi:10.1097/TA.0b013e3181961da2. discussion 296–287.

Doctor, J., Castro, J., Temkin, N., Fraser, R., Machamer, J., & Dikmen, S. (2005). Workers' risk of unemployment after traumatic brain injury: A normed comparison. *Journal of the International Neuropsychological Society, 11*(6), 747–752.

Doezema, D., King, J. N., Tandberg, D., Espinosa, M. C., & Orrison, W. W. (1991). Magnetic resonance imaging in minor head injury. *Annals of Emergency Medicine, 20*(12), 1281–1285.

Drew, L. B., & Drew, W. E. (2004). The contrecoup-coup phenomenon: A new understanding of the mechanism of closed head injury. *Neurocritical Care, 1*(3), 385–390. doi:10.1385/ncc:1:3:385.

Duma, S. M., Manoogian, S. J., Bussone, W. R., Brolinson, P. G., Goforth, M. W., Donnenwerth, J. J., et al. (2005). Analysis of real-time head accelerations in collegiate football players. *Clinical Journal of Sport Medicine, 15*(1), 3–8.

Dunham, C. M., Coates, S., & Cooper, C. (1996). Compelling evidence for discretionary brain computed tomographic imaging in those patients with mild cognitive impairment after blunt trauma. *The Journal of Trauma, 41*(4), 679–686.

Elder, G. A., & Cristian, A. (2009). Blast-related mild traumatic brain injury: Mechanisms of injury and impact on clinical care. *The Mount Sinai Journal of Medicine, 76*(2), 111–118. doi:10.1002/msj.20098.

Elder, G. A., Mitsis, E. M., Ahlers, S. T., & Cristian, A. (2010). Blast-induced mild traumatic brain injury. *Psychiatric Clinics of North America, 33*(4), 757–781. doi:10.1016/j.psc.2010.08.001.

Elliott, M. R., Arbogast, K. A., & Durbin, D. R. (2006). A latent class analysis of injury patterns among rear-seated, seat-belted children. *The Journal of Trauma, 61*(5), 1244–1248. doi:10.1097/01.ta.0000195983.48529.0d.

Eppinger, R., Sun, E., Bandak, F., Haffner, M., Khaewpong, N., Maltese, M., et al. (1999). Development of improved injury criteria for the assessment of advanced automotive restraint systems–II. *National Highway Traffic Safety Administration*.

Esselman, P. C., & Uomoto, J. (1995). Classification of the spectrum of mild traumatic brain injury. *Brain Injury, 9*(4), 417–424.

Fann, J. R., Burington, B., Leonetti, A., Jaffe, K., Katon, W. J., & Thompson, R. S. (2004). Psychiatric illness following traumatic brain injury in an adult health maintenance organization population. *Archives of General Psychiatry, 61*(1), 53–61. doi:10.1001/archpsyc.61.1.53.

Farace, E., & Alves, W. M. (2000). Do women fare worse: A metaanalysis of gender differences in traumatic brain injury outcome. *Journal of Neurosurgery, 93*(4), 539–545. doi:10.3171/jns.2000.93.4.0539.

Fay, T. B., Yeates, K. O., Taylor, H. G., Bangert, B., Dietrich, A., Nuss, K. E., et al. (2010). Cognitive reserve as a moderator of postconcussive symptoms in children with complicated and uncomplicated mild traumatic brain injury. *Journal of the International Neuropsychological Society, 16*(1), 94–105. doi:10.1017/s1355617709991007.

Fenton, G., McClelland, R., Montgomery, A., MacFlynn, G., & Rutherford, W. (1993). The postconcussional syndrome: Social antecedents and psychological sequelae. *The British Journal of Psychiatry, 162*, 493–497.

Field, M., Collins, M. W., Lovell, M. R., & Maroon, J. (2003). Does age play a role in recovery from sports-related concussion? a comparison of high school and collegiate athletes. *Journal of Pediatrics, 142*(5), 546–553. doi:10.1067/mpd.2003.190.

Frencham, K. A., Fox, A. M., & Maybery, M. T. (2005). Neuropsychological studies of mild traumatic brain injury: A meta-analytic review of research since 1995. *Journal of Clinical and Experimental Neuropsychology, 27*(3), 334–351. doi:10.1080/13803390490520328.

Friedland, J. F., & Dawson, D. R. (2001). Function after motor vehicle accidents: A prospective study of mild head injury and posttraumatic stress. *The Journal of Nervous and Mental Disease, 189*(7), 426–434.

Gaetz, M., Goodman, D., & Weinberg, H. (2000). Electrophysiological evidence for the cumulative effects of concussion. *Brain Injury, 14*(12), 1077–1088.

Gomez, P. A., Lobato, R. D., Ortega, J. M., & De La Cruz, J. (1996). Mild head injury: Differences in prognosis among patients with a Glasgow Coma Scale score of 13 to 15 and analysis of factors associated with abnormal CT findings. *British Journal of Neurosurgery, 10*(5), 453–460.

Gosselin, N., Bottari, C., Chen, J. K., Petrides, M., Tinawi, S., de Guise, E., et al. (2011). Electrophysiology and functional MRI in post-acute mild traumatic brain injury. *Journal of Neurotrauma, 28*(3), 329–341. doi:10.1089/neu.2010.1493.

Grady, M. F. (2010). Concussion in the adolescent athlete. *Current Problems in Pediatric and Adolescent Health Care, 40*(7), 154–169. doi:10.1016/j.cppeds.2010.06.002.

Graham, D. I., Ford, I., Adams, J. H., Doyle, D., Teasdale, G. M., Lawrence, A. E., et al. (1989). Ischaemic brain damage is still common in fatal non-missile head injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 52*(3), 346–350.

Greenwald, R. M., Gwin, J. T., Chu, J. J., & Crisco, J. J. (2008). Head impact severity measures for evaluating mild traumatic brain injury risk exposure. *Neurosurgery, 62*(4), 789–798. doi:10.1227/01.neu.0000318162.67472.ad. discussion 798.

Gronwall, D. (1991). Minor head injury. *Neuropsychology, 5*(4), 253.

Gross, H., Kling, A., Henry, G., Herndon, C., & Lavretsky, H. (1996). Local cerebral glucose metabolism in patients with long-term behavioral and cognitive deficits following mild traumatic brain injury. *The Journal of Neuropsychiatry and Clinical Neurosciences, 8*(3), 324–334.

Guskiewicz, K. M., McCrea, M., Marshall, S. W., Cantu, R. C., Randolph, C., Barr, W., et al. (2003). Cumulative effects associated with recurrent concussion in collegiate football players: The NCAA Concussion Study. *JAMA: The Journal of the American Medical Association, 290*(19), 2549–2555. doi:10.1001/jama.290.19.2549.

Hajek, C. A., Yeates, K. O., Gerry Taylor, H., Bangert, B., Dietrich, A., Nuss, K. E., et al. (2010). Relationships among post-concussive symptoms and symptoms of PTSD in children following mild traumatic brain injury. *Brain Injury, 24*(2), 100–109. doi:10.3109/02699050903508226.

Halterman, C. I., Langan, J., Drew, A., Rodriguez, E., Osternig, L. R., Chou, L. S., et al. (2006). Tracking the recovery of visuospatial attention deficits in mild traumatic brain injury. *Brain, 129*(Pt 3), 747–753. doi:10.1093/brain/awh705.

Harad, F. T., & Kerstein, M. D. (1992). Inadequacy of bedside clinical indicators in identifying significant intracranial injury in trauma patients. *The Journal of Trauma, 32*(3), 359–361. discussion 361–353.

Hault-dubrulle, A., Robache, F., Drazetic, P., Guillemot, H., & Morvan, H. (2011). Determination of pre-impact occupant postures and analysis of consequences on injury outcome–part II: Biomechanical study. *Accident Analysis and Prevention, 43*(1), 75–81.

Haydel, M. J., Preston, C. A., Mills, T. J., Luber, S., Blaudeau, E., & DeBlieux, P. M. (2000). Indications for computed tomography in patients with minor head injury. *The New England Journal of Medicine, 343*(2), 100–105. doi:10.1056/nejm200007133430204.

Hinton-Bayre, A. D., & Geffen, G. (2002). Severity of sports-related concussion and neuropsychological test performance. *Neurology, 59*(7), 1068–1070.

Hoge, C. W., McGurk, D., Thomas, J. L., Cox, A. L., Engel, C. C., & Castro, C. A. (2008). Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *The New England Journal of Medicine, 358*(5), 453–463. doi:10.1056/NEJMoa072972.

Huang, M. X., Theilmann, R. J., Robb, A., Angeles, A., Nichols, S., Drake, A., et al. (2009). Integrated imaging approach with MEG and DTI to detect mild traumatic brain injury in military and civilian patients. *Journal of Neurotrauma, 26*(8), 1213–1226. doi:10.1089/neu.2008.0672.

Hulkower, M. B., Zimmerman, M. E., Ackerman, N., Lipton, R. B., M. L., L. (2011). *Personalized analysis of diffusion tensor imaging (DTI) differentially predicts cognitive performance in subacute mild traumatic brain injury (mTBI).* Paper presented at the American Academy of Neurology, Honolulu, Hawaii.

Humayun, M. S., Presty, S. K., Lafrance, N. D., Holcomb, H. H., Loats, H., Long, D. M., et al. (1989). Local cerebral glucose abnormalities in mild closed head injured patients with cognitive impairments. *Nuclear Medicine Communications, 10*(5), 335–344.

Hutchinson, P. J., O'Connell, M. T., Rothwell, N. J., Hopkins, S. J., Nortje, J., Carpenter, K. L. H., et al. (2007). Inflammation in human brain injury: Intracerebral concentrations of IL-1 α, IL-1 β, and their endogenous inhibitor IL-1ra. *Journal of Neurotrauma, 24*(10), 1545–1557.

Ichise, M., Chung, D. G., Wang, P., Wortzman, G., Gray, B. G., & Franks, W. (1994). Technetium-99 m-HMPAO SPECT, CT and MRI in the evaluation of patients with chronic traumatic brain injury: A correlation with neuropsychological performance. *Journal of Nuclear Medicine, 35*(2), 217–226.

Inglese, M., Makani, S., Johnson, G., Cohen, B. A., Silver, J. A., Gonen, O., et al. (2005). Diffuse axonal injury in mild traumatic brain injury: A diffusion tensor imaging study. *Journal of Neurosurgery, 103*(2), 298–303. doi:10.3171/jns.2005.103.2.0298.

Iverson, G. L., Lovell, M. R., Smith, S., & Franzen, M. D. (2000). Prevalence of abnormal CT-scans following mild head injury. *Brain Injury, 14*(12), 1057–1061.

Iverson, G. L., Gaetz, M., Lovell, M. R., & Collins, M. W. (2004). Cumulative effects of concussion in amateur athletes. *Brain Injury, 18*(5), 433–443. doi:10.1080/02699050310001617352.

Ives, J. C., Alderman, M., & Stred, S. E. (2007). Hypopituitarism after multiple concussions: A retrospective case study in an adolescent male. *Journal of Athletic Training, 42*(3), 431–439.

Jacobs, B., Beems, T., Stulemeijer, M., van Vugt, A. B., van der Vliet, T. M., Borm, G. F., et al. (2010). Outcome prediction in mild traumatic brain injury: Age and clinical variables are stronger predictors than CT abnormalities. *Journal of Neurotrauma, 27*(4), 655–668. doi:10.1089/neu.2009.1059.

Johnstone, B., Hexum, C. L., & Ashkanazi, G. (1995). Extent of cognitive decline in traumatic brain injury based on estimates of premorbid intelligence. *Brain Injury, 9*(4), 377–384.

Kant, R., Smith-Seemiller, L., Isaac, G., & Duffy, J. (1997). Tc-HMPAO SPECT in persistent post-concussion syndrome after mild head injury: Comparison with MRI/CT. *Brain Injury, 11*(2), 115–124.

Kashluba, S., Hanks, R. A., Casey, J. E., & Millis, S. R. (2008). Neuropsychologic and functional outcome after complicated mild traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 89*(5), 904–911. doi:10.1016/j.apmr.2007.12.029.

Kashluba, S., Paniak, C., & Casey, J. E. (2008). Persistent symptoms associated with factors identified by the WHO Task Force on Mild Traumatic Brain Injury. *Clinical Neuropsychology, 22*(2), 195–208. doi:10.1080/13854040701263655.

Kelestimur, F. (2005). Chronic trauma in sports as a cause of hypopituitarism. *Pituitary, 8*(3–4), 259–262. doi:10.1007/s11102-006-6051-3.

Kelly, J., & Rosenberg, J. (1997). Practice parameter: The management of concussion in sports (summary statement). *Neurology, 48*(3), 581–585.

Kelly, M. P., Johnson, C. T., Knoller, N., Drubach, D. A., & Winslow, M. M. (1997). Substance abuse, traumatic brain injury and neuropsychological outcome. *Brain Injury, 11*(6), 391–402.

Kelly, D. F., McArthur, D. L., Levin, H., Swimmer, S., Dusick, J. R., Cohan, P., et al. (2006). Neurobehavioral and quality of life changes associated with growth hormone insufficiency after complicated mild, moderate, or severe traumatic brain injury. *Journal of Neurotrauma, 23*(6), 928–942. doi:10.1089/neu.2006.23.928.

Kim, J. J., & Gean, A. D. (2011). Imaging for the diagnosis and management of traumatic brain injury. *Neurotherapeutics, 8*(1), 39–53. doi:10.1007/s13311-010-0003-3.

Kim, N., H. M. B., Park, Y., Gardin, T. M., Smith, J. L., Branch, C. A., Lipton, M. L. (2011). *Robust detection of white matter injury in individual patients after mild traumatic brain injury.* Paper presented at the ISMRM, Montreal, Quebec, Canada,

King, A. I., & Yang, K. H. (1995). Research in biomechanics of occupant protection. *The Journal of Trauma, 38*(4), 570.

King, N. S., Crawford, S., Wenden, F. J., Moss, N. E., & Wade, D. T. (1995). The rivermead post concussion symptoms questionnaire: A measure of symptoms commonly experienced after head injury and its reliability. *Journal of Neurology, 242*(9), 587–592.

King, A. I., Yang, K. H., & Hardy, W. N. (2011). Recent firsts in cadaveric impact biomechanics research. *Clinical Anatomy, 24*(3), 294–308. doi:10.1002/ca.21151.

Kleiven, S. (2003). Influence of impact direction on the human head in prediction of subdural hematoma. *Journal of Neurotrauma, 20*(4), 365–379. doi:10.1089/089771503765172327.

Kolakowsky-Hayner, S. A., Gourley, E. V., 3rd, Kreutzer, J. S., Marwitz, J. H., Meade, M. A., & Cifu, D. X. (2002). Post-injury

substance abuse among persons with brain injury and persons with spinal cord injury. *Brain Injury, 16*(7), 583–592. doi:10.1080/02699050110119475.

Konrad, C., Geburek, A. J., Rist, F., Blumenroth, H., Fischer, B., Husstedt, I., et al. (2010). Long-term cognitive and emotional consequences of mild traumatic brain injury. *Psychological Medicine, 1–15*. doi:10.1017/s0033291710001728.

Koura, S., Doppenberg, E., Marmarou, A., Choi, S., Young, H., Bullock, R. (1998). Relationship between excitatory amino acid release and outcome after severe human head injury. In *vol. 71* (pp. 244–246). Springer Verlag.

Kraus, J. F., & Nourjah, P. (1988). The epidemiology of mild, uncomplicated brain injury. *The Journal of Trauma, 28*(12), 1637–1643.

Kraus, J. F., Morgenstern, H., Fife, D., Conroy, C., & Nourjah, P. (1989). Blood alcohol tests, prevalence of involvement, and outcomes following brain injury. *American Journal of Public Health, 79*(3), 294–299.

Kraus, J., Schaffer, K., Ayers, K., Stenehjem, J., Shen, H., & Afifi, A. A. (2005). Physical complaints, medical service use, and social and employment changes following mild traumatic brain injury: A 6-month longitudinal study. *The Journal of Head Trauma Rehabilitation, 20*(3), 239–256.

Kurca, E., Sivak, S., & Kucera, P. (2006). Impaired cognitive functions in mild traumatic brain injury patients with normal and pathologic magnetic resonance imaging. *Neuroradiology, 48*(9), 661–669. doi:10.1007/s00234-006-0109-9.

Landre, N., Poppe, C. J., Davis, N., Schmaus, B., & Hobbs, S. E. (2006). Cognitive functioning and postconcussive symptoms in trauma patients with and without mild TBI. *Archives of Clinical Neuropsychology, 21*(4), 255–273. doi:10.1016/j.acn.2005.12.007.

Lange, R. T., Iverson, G. L., & Franzen, M. D. (2007). Short-term neuropsychological outcome following uncomplicated mild TBI: Effects of day-of-injury intoxication and pre-injury alcohol abuse. *Neuropsychology, 21*(5), 590–598. doi:10.1037/0894-4105.21.5.590.

Langlois, J. A., Rutland-Brown, W., & Wald, M. M. (2006). The epidemiology and impact of traumatic brain injury: A brief overview. *The Journal of Head Trauma Rehabilitation, 21*(5), 375–378.

Lee, H., Wintermark, M., Gean, A. D., Ghajar, J., Manley, G. T., & Mukherjee, P. (2008). Focal lesions in acute mild traumatic brain injury and neurocognitive outcome: CT versus 3T MRI. *Journal of Neurotrauma, 25*(9), 1049–1056. doi:10.1089/neu.2008.0566.

Leininger, B. E., Gramling, S. E., Farrell, A. D., Kreutzer, J. S., & Peck, E. A., 3rd. (1990). Neuropsychological deficits in symptomatic minor head injury patients after concussion and mild concussion. *Journal of Neurology, Neurosurgery, and Psychiatry, 53*(4), 293–296.

Len, T. K., & Neary, J. P. (2011). Cerebrovascular pathophysiology following mild traumatic brain injury. *Clinical Physiology and Functional Imaging, 31*(2), 85–93. doi:10.1111/j.1475-097X.2010.00990.x.

Levin, H. S., Amparo, E., Eisenberg, H. M., Williams, D. H., High, W. M., Jr., McArdle, C. B., et al. (1987). Magnetic resonance imaging and computerized tomography in relation to the neurobehavioral sequelae of mild and moderate head injuries. *Journal of Neurosurgery, 66*(5), 706–713. doi:10.3171/jns.1987.66.5.0706.

Levin, H. S., Hanten, G., Roberson, G., Li, X., Ewing-Cobbs, L., Dennis, M., et al. (2008). Prediction of cognitive sequelae based on abnormal computed tomography findings in children following mild traumatic brain injury. *Journal of Neurosurgery. Pediatrics, 1*(6), 461–470. doi:10.3171/ped/2008/1/6/461.

Liberman, J. N., Stewart, W. F., Wesnes, K., & Troncoso, J. (2002). Apolipoprotein E epsilon 4 and short-term recovery from predominantly mild brain injury. *Neurology, 58*(7), 1038–1044.

Lipton, M. L., Gellella, E., Lo, C., Gold, T., Ardekani, B. A., Shifteh, K., et al. (2008). Multifocal white matter ultrastructural abnormalities in mild traumatic brain injury with cognitive disability: A voxel-wise analysis of diffusion tensor imaging. *Journal of Neurotrauma, 25*(11), 1335–1342. doi:10.1089/neu.2008.0547.

Lipton, M. L., Gulko, E., Zimmerman, M. E., Friedman, B. W., Kim, M., Gellella, E., et al. (2009). Diffusion-tensor imaging implicates prefrontal axonal injury in executive function impairment following very mild traumatic brain injury. *Radiology, 252*(3), 816–824. doi:10.1148/radiol.2523081584.

Lipton, M. L., Kim, N., Park Y. K., Hulkower M. B., Gardin, T. M., Shifteh, K., et al. (2012). Robust detection of traumatic axonal injury in individual mild traumatic brain injury patients: Intersubject variation, change over time and bidirectional changes in anisotropy. *Brain Imaging and Behavior*. This special issue.

Luis, C. A., Vanderploeg, R. D., & Curtiss, G. (2003). Predictors of postconcussion symptom complex in community dwelling male veterans. *Journal of the International Neuropsychological Society, 9*(7), 1001–1015.

Lundin, A., de Boussard, C., Edman, G., & Borg, J. (2006). Symptoms and disability until 3 months after mild TBI. *Brain Injury, 20*(8), 799–806. doi:10.1080/02699050600744327.

MacMillan, P. J., Hart, R. P., Martelli, M. F., & Zasler, N. D. (2002). Pre-injury status and adaptation following traumatic brain injury. *Brain Injury, 16*(1), 41–49. doi:10.1080/0269905011008812.

Maddocks, D. L., Saling, M., & Dicker, G. D. (1995). A note on normative data for a test sensitive to concussion in Australian rules footballers. *Australian Psychologist, 30*(2), 125–127.

Margulies, S., & Hicks, R. (2009). Combination therapies for traumatic brain injury: Prospective considerations. *Journal of Neurotrauma, 26*(6), 925–939.

McAllister, T. W., Sparling, M. B., Flashman, L. A., & Saykin, A. J. (2001). Neuroimaging findings in mild traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology, 23*(6), 775–791. doi:10.1076/jcen.23.6.775.1026.

McCauley, S. R., Boake, C., Levin, H. S., Contant, C. F., & Song, J. X. (2001). Postconcussional disorder following mild to moderate traumatic brain injury: Anxiety, depression, and social support as risk factors and comorbidities. *Journal of Clinical and Experimental Neuropsychology, 23*(6), 792–808. doi:10.1076/jcen.23.6.792.1016.

McClincy, M. P., Lovell, M. R., Pardini, J., Collins, M. W., & Spore, M. K. (2006). Recovery from sports concussion in high school and collegiate athletes. *Brain Injury, 20*(1), 33–39. doi:10.1080/02699050500309817.

McCrea, M., Iverson, G. L., McAllister, T. W., Hammeke, T. A., Powell, M. R., Barr, W. B., et al. (2009). An integrated review of recovery after mild traumatic brain injury (MTBI): Implications for clinical management. *The Clinical Neuropsychologist*.

McCrory, P., Meeuwisse, W., Johnston, K., Dvorak, J., Aubry, M., Molloy, M., et al. (2009). Consensus statement on concussion in sport–the 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *South African Journal of Sports Medicine, 21*(2).

McGowan, J. C., Yang, J. H., Plotkin, R. C., Grossman, R. I., Umile, E. M., Cecil, K. M., et al. (2000). Magnetization transfer imaging in the detection of injury associated with mild head trauma. *AJNR. American Journal of Neuroradiology, 21*(5), 875–880.

McKeever, C. K., & Schatz, P. (2003). Current issues in the identification, assessment, and management of concussions in sports-related injuries. *Applied Neuropsychology, 10*(1), 4–11. doi:10.1207/s15324826an1001_2.

Meaney, D. F., & Smith, D. H. (2011). Biomechanics of concussion. *Clinics in Sports Medicine, 30*(1), 19–31. doi:10.1016/j.csm.2010.08.009. vii.

Meares, S., Shores, E. A., Taylor, A. J., Batchelor, J., Bryant, R. A., Baguley, I. J., et al. (2008). Mild traumatic brain injury does not

predict acute postconcussion syndrome. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(3), 300–306. doi:10.1136/jnnp.2007.126565.

Mellergård, P., Åneman, O., Sjögren, F., Säberg, C., & Hillman, J. (2011). Differences in cerebral extracellular response of interleukin-1β, interleukin-6, and interleukin-10 after subarachnoid hemorrhage or severe head trauma in humans. *Neurosurgery, 68*(1), 12.

Montgomery, E. A., Fenton, G. W., McClelland, R. J., MacFlynn, G., & Rutherford, W. H. (1991). The psychobiology of minor head injury. *Psychological Medicine, 21*(2), 375–384.

Mooney, G., & Speed, J. (2001). The association between mild traumatic brain injury and psychiatric conditions. *Brain Injury, 15*(10), 865–877. doi:10.1080/02699050110065286.

Moran, L. M., Taylor, H. G., Ganesalingam, K., Gastier-Foster, J. M., Frick, J., Bangert, B., et al. (2009). Apolipoprotein E4 as a predictor of outcomes in pediatric mild traumatic brain injury. *Journal of Neurotrauma, 26*(9), 1489–1495. doi:10.1089/neu.2008.0767.

Moriarity, J., Collie, A., Olson, D., Buchanan, J., Leary, P., McStephen, M., et al. (2004). A prospective controlled study of cognitive function during an amateur boxing tournament. *Neurology, 62*(9), 1497–1502.

Mosenthal, A. C., Livingston, D. H., Lavery, R. F., Knudson, M. M., Lee, S., Morabito, D., et al. (2004). The effect of age on functional outcome in mild traumatic brain injury: 6-month report of a prospective multicenter trial. *The Journal of Trauma, 56*(5), 1042–1048.

Nedd, K., Sfakianakis, G., Ganz, W., Uricchio, B., Vernberg, D., Villanueva, P., et al. (1993). 99mTc-HMPAO SPECT of the brain in mild to moderate traumatic brain injury patients: Compared with CT–a prospective study. *Brain Injury, 7*(6), 469–479.

Newman, J., Barr, C., Beusenberg, M., Fournier, E., Shewchenko, N., Welbourne, E., et al. (2000). A new biomechanical assessment of mild traumatic brain injury. Part 2: results and conclusions. In.

Niogi, S. N., & Mukherjee, P. (2010). Diffusion tensor imaging of mild traumatic brain injury. *The Journal of Head Trauma Rehabilitation, 25*(4), 241–255. doi:10.1097/HTR.0b013e3181e52c2a.

Niogi, S., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R., Sarkar, R., et al. (2008). Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: A 3T diffusion tensor imaging study of mild traumatic brain injury. *AJNR. American Journal of Neuroradiology, 29*(5), 967.

Nolle, C., Todt, I., Seidl, R. O., & Ernst, A. (2004). Pathophysiological changes of the central auditory pathway after blunt trauma of the head. *Journal of Neurotrauma, 21*(3), 251–258. doi:10.1089/089771504322972040.

Oehmichen, M., Walter, T., Meissner, C., & Friedrich, H. J. (2003). Time course of cortical hemorrhages after closed traumatic brain injury: Statistical analysis of posttraumatic histomorphological alterations. *Journal of Neurotrauma, 20*(1), 87–103. doi:10.1089/08977150360517218.

Ommaya, A., Goldsmith, W., & Thibault, L. (2002). Biomechanics and neuropathology of adult and paediatric head injury. *British Journal of Neurosurgery, 16*(3), 220–242.

Paniak, C., Toller-Lobe, G., Melnyk, A., & Nagy, J. (2000). Prediction of vocational status 3 to 4 months after treated mild traumatic brain injury. *Journal of Musculoskeletal Pain, 8*(1–2), 193–200.

Patterson, J. H., Jr., & Hamernik, R. P. (1997). Blast overpressure induced structural and functional changes in the auditory system. *Toxicology, 121*(1), 29–40.

Pellman, E. J., Viano, D. C., Tucker, A. M., & Casson, I. R. (2003). Concussion in professional football: Location and direction of helmet impacts-part 2. *Neurosurgery, 53*(6), 1328–1340. discussion 1340–1321.

Pertab, J. L., James, K. M., & Bigler, E. D. (2009). Limitations of mild traumatic brain injury meta-analyses. *Brain Injury, 23*(6), 498–508. doi:10.1080/02699050902927984.

Peterson, T. D., Jolly, B. T., Runge, J. W., & Hunt, R. C. (1999). Motor vehicle safety: Current concepts and challenges for emergency physicians. *Annals of Emergency Medicine, 34*(3), 384–393.

Peterson, S. E., Stull, M. J., Collins, M. W., & Wang, H. E. (2009). Neurocognitive function of emergency department patients with mild traumatic brain injury. *Annals of Emergency Medicine, 53*(6), 796 e791–803 e791. doi:10.1016/j.annemergmed.2008.10.015.

Ponsford, J., Willmott, C., Rothwell, A., Cameron, P., Kelly, A. M., Nelms, R., et al. (2000). Factors influencing outcome following mild traumatic brain injury in adults. *Journal of the International Neuropsychological Society, 6*(5), 568–579.

Ponsford, J., Cameron, P., Fitzgerald, M., Grant, M., & Mikocka-Walus, A. (2011). Long-term outcomes after uncomplicated mild traumatic brain injury: A comparison with trauma controls. *Journal of Neurotrauma, 28*(6), 937–946. doi:10.1089/neu.2010.1516.

Pruthi, N., Chandramouli, B. A., Kuttappa, T. B., Rao, S. L., Subbakrishna, D. K., Abraham, M. P., et al. (2010). Apolipoprotein E polymorphism and outcome after mild to moderate traumatic brain injury: A study of patient population in India. *Neurology India, 58*(2), 264–269. doi:10.4103/0028-3886.63810.

Reed, N., Taha, T., Keightley, M., Duggan, C., McAuliffe, J., Cubos, J., et al. (2010). Measurement of head impacts in youth ice hockey players. *International Journal of Sports Medicine, 31*(11), 826–833. doi:10.1055/s-0030-1263103.

Rimel, R. W., Giordani, B., Barth, J. T., Boll, T. J., & Jane, J. A. (1981). Disability caused by minor head injury. *Neurosurgery, 9*(3), 221–228.

Rosenfeld, J. V., & Ford, N. L. (2010). Bomb blast, mild traumatic brain injury and psychiatric morbidity: A review. *Injury, 41*(5), 437–443. doi:10.1016/j.injury.2009.11.018.

Rosenthal, M., Dljkers, M., Harrison-Felix, C., Nabors, N., Witol, A. D., Young, M. E., et al. (1996). Impact of minority status on functional outcome and community integration following traumatic brain injury. *The Journal of Head Trauma Rehabilitation, 11*(5), 40.

Roudsari, B. S., Mock, C. N., Kaufman, R., Grossman, D., Henary, B. Y., & Crandall, J. (2004). Pedestrian crashes: Higher injury severity and mortality rate for light truck vehicles compared with passenger vehicles. *Injury Prevention, 10*(3), 154–158.

Ruff, R. M. (2011). Mild traumatic brain injury and neural recovery: Rethinking the debate. *NeuroRehabilitation, 28*(3), 167–180. doi:10.3233/nre-2011-0646.

Ruff, R. M., Marshall, L. F., Klauber, M. R., Blunt, B. A. (1990). Alcohol abuse and neurological outcome of the severely head injured. *The Journal of Head Trauma Rehabilitation*.

Ruff, R. M., Camenzuli, L., & Mueller, J. (1996). Miserable minority: Emotional risk factors that influence the outcome of a mild traumatic brain injury. *Brain Injury, 10*(8), 551–565.

Rutgers, D., Toulgoat, F., Cazejust, J., Fillard, P., Lasjaunias, P., & Ducreux, D. (2008). White matter abnormalities in mild traumatic brain injury: A diffusion tensor imaging study. *AJNR. American Journal of Neuroradiology, 29*(3), 514.

Saatman, K. E., Duhaime, A. C., Bullock, R., Maas, A. I., Valadka, A., & Manley, G. T. (2008). Classification of traumatic brain injury for targeted therapies. *Journal of Neurotrauma, 25*(7), 719–738. doi:10.1089/neu.2008.0586.

Sabet, A. A., Christoforou, E., Zatlin, B., Genin, G. M., & Bayly, P. V. (2008). Deformation of the human brain induced by mild angular head acceleration. *Journal of Biomechanics, 41*(2), 307–315. doi:10.1016/j.jbiomech.2007.09.016.

Salmond, C., Menon, D., Chatfield, D., Williams, G., Pena, A., Sahakian, B., et al. (2006). Diffusion tensor imaging in chronic head injury survivors: Correlations with learning and memory indices. *NeuroImage, 29*(1), 117–124.

Scheid, R., Preul, C., Gruber, O., Wiggins, C., & von Cramon, D. Y. (2003). Diffuse axonal injury associated with chronic traumatic brain injury: Evidence from T2*-weighted gradient-echo imaging at 3T. *AJNR. American Journal of Neuroradiology, 24*(6), 1049–1056.

Schneider, H. J., Kreitschmann-Andermahr, I., Ghigo, E., Stalla, G. K., & Agha, A. (2007). Hypothalamopituitary dysfunction following traumatic brain injury and aneurysmal subarachnoid hemorrhage: A systematic review. *JAMA: The Journal of the American Medical Association, 298*(12), 1429–1438. doi:10.1001/jama.298.12.1429.

Schretlen, D. J., & Shapiro, A. M. (2003). A quantitative review of the effects of traumatic brain injury on cognitive functioning. *International Review of Psychiatry, 15*(4), 341–349. doi:10.1080/09540260310001606728.

Schwartz, I., Tuchner, M., Tsenter, J., Shochina, M., Shoshan, Y., Katz-Leurer, M., et al. (2008). Cognitive and functional outcomes of terror victims who suffered from traumatic brain injury. *Brain Injury, 22*(3), 255–263. doi:10.1080/02699050801941763.

Scott Delaney, J., Puni, V., & Rouah, F. (2006). Mechanisms of injury for concussions in university football, ice hockey, and soccer: A pilot study. *Clinical Journal of Sport Medicine, 16*(2), 162–165.

Servadei, F., Teasdale, G., & Merry, G. (2001). Defining acute mild head injury in adults: A proposal based on prognostic factors, diagnosis, and management. *Journal of Neurotrauma, 18*(7), 657–664. doi:10.1089/089771501750357609.

Shenton, M. E., Hamoda, H. M., Schneiderman, J. S., Bouix, S., Pasternak, O., Rathi, Y., et al. (2012). A review of magnetic resonance imaging and diffusion tensor imaging findings in mild traumatic brain injury. *Brain Imaging and Behavior*. This special issue.

Shores, E. A., Lammel, A., Hullick, C., Sheedy, J., Flynn, M., Levick, W., et al. (2008). The diagnostic accuracy of the Revised Westmead PTA Scale as an adjunct to the Glasgow Coma Scale in the early identification of cognitive impairment in patients with mild traumatic brain injury. *Journal of Neurology, Neurosurgery, and Psychiatry, 79*(10), 1100–1106. doi:10.1136/jnnp. 2007.132571.

Shukla, D., & Devi, B. I. (2010). Mild traumatic brain injuries in adults. *Journal of Neurosciences in Rural Practice, 1*(2), 82–88. doi:10.4103/0976-3147.71723.

Signoretti, S., Vagnozzi, R., Tavazzi, B., & Lazzarino, G. (2010). Biochemical and neurochemical sequelae following mild traumatic brain injury: Summary of experimental data and clinical implications. *Neurosurgical Focus, 29*(5), E1. doi:10.3171/2010.9.focus10183.

Sinson, G., Bagley, L. J., Cecil, K. M., Torchia, M., McGowan, J. C., Lenkinski, R. E., et al. (2001). Magnetization transfer imaging and proton MR spectroscopy in the evaluation of axonal injury: Correlation with clinical outcome after traumatic brain injury. *AJNR. American Journal of Neuroradiology, 22*(1), 143–151.

Sroufe, N. S., Fuller, D. S., West, B. T., Singal, B. M., Warschausky, S. A., & Maio, R. F. (2010). Postconcussive symptoms and neurocognitive function after mild traumatic brain injury in children. *Pediatrics, 125*(6), e1331–e1339. doi:10.1542/peds.2008-2364.

Stambrook, M., Moore, A. D., Peters, L. C., Deviaene, C., & Hawryluk, G. A. (1990). Effects of mild, moderate and severe closed head injury on long-term vocational status. *Brain Injury, 4*(2), 183–190.

Stapert, S., Houx, P., de Kruijk, J., Ponds, R., & Jolles, J. (2006). Neurocognitive fitness in the sub-acute stage after mild TBI: The effect of age. *Brain Injury, 20*(2), 161–165. doi:10.1080/02699050500442949.

Stein, D. G., & Hoffman, S. W. (2003). Estrogen and progesterone as neuroprotective agents in the treatment of acute brain injuries. *Developmental Neurorehabilitation, 6*(1), 13–22.

Sterr, A., Herron, K. A., Hayward, C., & Montaldi, D. (2006). Are mild head injuries as mild as we think? neurobehavioral concomitants of chronic post-concussion syndrome. *BMC Neurology, 6*, 7. doi:10.1186/1471-2377-6-7.

Stevens, M. C., Lovejoy, D., Kim, J., Oakes, H., Kureshi, I., & Witt, S. T. (2012). Multiple resting state network functional connectivity abnormalities in mild traumatic brain injury. *Brain Imaging and Behavior*. This special issue.

Styrke, J., Stalnacke, B. M., Sojka, P., & Bjornstig, U. (2007). Traumatic brain injuries in a well-defined population: Epidemiological aspects and severity. *Journal of Neurotrauma, 24*(9), 1425–1436. doi:10.1089/neu.2007.0266.

Suh, M., Basu, S., Kolster, R., Sarkar, R., McCandliss, B., & Ghajar, J. (2006). Increased oculomotor deficits during target blanking as an indicator of mild traumatic brain injury. *Neuroscience Letters, 410*(3), 203–207. doi:10.1016/j.neulet.2006.10.001.

Suhr, J., Tranel, D., Wefel, J., & Barrash, J. (1997). Memory performance after head injury: Contributions of malingering, litigation status, psychological factors, and medication use. *Journal of Clinical and Experimental Neuropsychology, 19*(4), 500–514.

Sundstrom, A., Marklund, P., Nilsson, L. G., Cruts, M., Adolfsson, R., Van Broeckhoven, C., et al. (2004). APOE influences on neuropsychological function after mild head injury: Within-person comparisons. *Neurology, 62*(11), 1963–1966.

Tait, R. J., Anstey, K. J., & Butterworth, P. (2010). Incidence of self-reported brain injury and the relationship with substance abuse: Findings from a longitudinal community survey. *BMC Public Health, 10*, 171. doi:10.1186/1471-2458-10-171.

Tanriverdi, F., Unluhizarci, K., Coksevim, B., Selcuklu, A., Casanueva, F. F., & Kelestimur, F. (2007). Kickboxing sport as a new cause of traumatic brain injury-mediated hypopituitarism. *Clinical Endocrinology, 66*(3), 360–366. doi:10.1111/j.1365-2265.2006.02737.x.

Tanriverdi, F., Unluhizarci, K., & Kelestimur, F. (2010). Pituitary function in subjects with mild traumatic brain injury: A review of literature and proposal of a screening strategy. *Pituitary, 13*(2), 146–153. doi:10.1007/s11102-009-0215-x.

Taylor, H. G., Dietrich, A., Nuss, K., Wright, M., Rusin, J., Bangert, B., et al. (2010). Post-concussive symptoms in children with mild traumatic brain injury. *Neuropsychology, 24*(2), 148–159. doi:10.1037/a0018112.

Teasdale, T. W., & Engberg, A. W. (2003). Cognitive dysfunction in young men following head injury in childhood and adolescence: A population study. *Journal of Neurology, Neurosurgery, and Psychiatry, 74*(7), 933–936.

Teasdale, G. M., Nicoll, J. A., Murray, G., & Fiddes, M. (1997). Association of apolipoprotein E polymorphism with outcome after head injury. *Lancet, 350*(9084), 1069–1071. doi:10.1016/s0140-6736(97)04318-3.

Tellier, A., Marshall, S. C., Wilson, K. G., Smith, A., Perugini, M., & Stiell, I. G. (2009). The heterogeneity of mild traumatic brain injury: Where do we stand? *Brain Injury, 23*(11), 879–887. doi:10.1080/02699050903200555.

Terrell, T. R., Bostick, R. M., Abramson, R., Xie, D., Barfield, W., Cantu, R., et al. (2008). APOE, APOE promoter, and Tau genotypes and risk for concussion in college athletes. *Clinical Journal of Sport Medicine, 18*(1), 10–17. doi:10.1097/JSM.0b013e31815c1d4c.

Theriault, M., De Beaumont, L., Tremblay, S., Lassonde, M., & Jolicoeur, P. (2011). Cumulative effects of concussions in athletes revealed by electrophysiological abnormalities on visual working memory. *Journal of Clinical and Experimental Neuropsychology, 33*(1), 30–41. doi:10.1080/13803391003772873.

Thornhill, S., Teasdale, G. M., Murray, G. D., McEwen, J., Roy, C. W., & Penny, K. I. (2000). Disability in young people and adults 1 year after head injury: Prospective cohort study. *BMJ, 320*(7250), 1631–1635.

Tierney, R. T., Mansell, J. L., Higgins, M., McDevitt, J. K., Toone, N., Gaughan, J. P., et al. (2010). Apolipoprotein E

genotype and concussion in college athletes. *Clinical Journal of Sport Medicine, 20*(6), 464–468. doi:10.1097/JSM.0b013e3181fc0a81.

Tung, G. A., Kumar, M., Richardson, R. C., Jenny, C., & Brown, W. D. (2006). Comparison of accidental and nonaccidental traumatic head injury in children on noncontrast computed tomography. *Pediatrics, 118*(2), 626.

Tureci, E., Dashti, R., Tanriverdi, T., Sanus, G. Z., Oz, B., & Uzan, M. (2004). Acute ethanol intoxication in a model of traumatic brain injury: The protective role of moderate doses demonstrated by immunoreactivity of synaptophysin in hippocampal neurons. *Neurological Research, 26*(1), 108–112.

Umile, E. M., Sandel, M. E., Alavi, A., Terry, C. M., & Plotkin, R. C. (2002). Dynamic imaging in mild traumatic brain injury: Support for the theory of medial temporal vulnerability. *Archives of Physical Medicine and Rehabilitation, 83*(11), 1506–1513.

van Donkelaar, P., Langan, J., Rodriguez, E., Drew, A., Halterman, C., Osternig, L. R., et al. (2005). Attentional deficits in concussion. *Brain Injury, 19*(12), 1031–1039. doi:10.1080/02699050500110363.

Vanderploeg, R. D., Curtiss, G., Duchnick, J. J., & Luis, C. A. (2003). Demographic, medical, and psychiatric factors in work and marital status after mild head injury. *The Journal of Head Trauma Rehabilitation, 18*(2), 148–163.

Vanderploeg, R. D., Curtiss, G., & Belanger, H. G. (2005). Long-term neuropsychological outcomes following mild traumatic brain injury. *Journal of the International Neuropsychological Society, 11*(3), 228–236. doi:10.1017/s1355617705050289.

Vanderploeg, R. D., Curtiss, G., Luis, C. A., & Salazar, A. M. (2007). Long-term morbidities following self-reported mild traumatic brain injury. *Journal of Clinical and Experimental Neuropsychology, 29*(6), 585–598. doi:10.1080/13803390600826587.

Viano, D. C., Casson, I. R., Pellman, E. J., Zhang, L., King, A. I., & Yang, K. H. (2005). Concussion in professional football: Brain responses by finite element analysis: Part 9. *Neurosurgery, 57*(5), 891–916. discussion 891–916.

Viano, D. C., Casson, I. R., & Pellman, E. J. (2007). Concussion in professional football: Biomechanics of the struck player—part 14. *Neurosurgery, 61*(2), 313–327. doi:10.1227/01.neu.0000279969.02685.d0. discussion 327–318.

Vickery, C. D., Sherer, M., Nick, T. G., Nakase-Richardson, R., Corrigan, J. D., Hammond, F., et al. (2008). Relationships among premorbid alcohol use, acute intoxication, and early functional status after traumatic brain injury. *Archives of Physical Medicine and Rehabilitation, 89*(1), 48–55. doi:10.1016/j.apmr.2007.07.047.

Voller, B., Benke, T., Benedetto, K., Schnider, P., Auff, E., & Aichner, F. (1999). Neuropsychological, MRI and EEG findings after very mild traumatic brain injury. *Brain Injury, 13*(10), 821–827.

Vos, P., Battistin, L., Birbamer, G., Gerstenbrand, F., Potapov, A., Prevec, T., et al. (2002). EFNS guideline on mild traumatic brain injury: Report of an EFNS task force. *European Journal of Neurology, 9*(3), 207–219.

Walilko, T., Viano, D., & Bir, C. (2005). Biomechanics of the head for Olympic boxer punches to the face. *British Journal of Sports Medicine, 39*(10), 710.

Wall, S. E., Williams, W. H., Cartwright-Hatton, S., Kelly, T. P., Murray, J., Murray, M., et al. (2006). Neuropsychological dysfunction following repeat concussions in jockeys. *Journal of Neurology, Neurosurgery, and Psychiatry, 77*(4), 518–520. doi:10.1136/jnnp. 2004.061044.

Webb, C. R., Wrigley, M., Yoels, W., & Fine, P. R. (1995). Explaining quality of life for persons with traumatic brain injuries 2 years after injury. *Archives of Physical Medicine and Rehabilitation, 76*(12), 1113–1119.

Whelan-Goodinson, R., Ponsford, J., Johnston, L., & Grant, F. (2009). Psychiatric disorders following traumatic brain injury: Their nature and frequency. *The Journal of Head Trauma Rehabilitation, 24*(5), 324–332. doi:10.1097/HTR.0b013e3181a712aa.

Williams, D. H., Levin, H. S., & Eisenberg, H. M. (1990). Mild head injury classification. *Neurosurgery, 27*(3), 422.

Williams, W. H., Potter, S., & Ryland, H. (2010). Mild traumatic brain injury and Postconcussion syndrome: A neuropsychological perspective. *Journal of Neurology, Neurosurgery, and Psychiatry, 81*(10), 1116–1122. doi:10.1136/jnnp. 2008.171298.

Xydakis, M. S., Bebarta, V. S., Harrison, C. D., Conner, J. C., Grant, G. A., & Robbins, A. S. (2007). Tympanic-membrane perforation as a marker of concussive brain injury in Iraq. *The New England Journal of Medicine, 357*(8), 830–831. doi:10.1056/NEJMc076071.

Yeates, K. O. (2010). Mild traumatic brain injury and postconcussive symptoms in children and adolescents. *Journal of the International Neuropsychological Society, 16*(6), 953–960. doi:10.1017/s1355617710000986.

Yoganandan, N., Pintar, F. A., Zhang, J., & Baisden, J. L. (2009). Physical properties of the human head: Mass, center of gravity and moment of inertia. *Journal of Biomechanics, 42*(9), 1177–1192. doi:10.1016/j.jbiomech.2009.03.029.

Zappala, G., Thiebaut de Schotten, M., & Eslinger, P. J. (2011). Traumatic brain injury and the frontal lobes: What can we gain with diffusion tensor imaging? *Cortex*. doi:10.1016/j.cortex.2011.06.020.

Zhou, W., Xu, D., Peng, X., Zhang, Q., Jia, J., & Crutcher, K. A. (2008). Meta-analysis of APOE4 allele and outcome after traumatic brain injury. *Journal of Neurotrauma, 25*(4), 279–290. doi:10.1089/neu.2007.0489.

Zitnay, G. A., Zitnay, K. M., Povlishock, J. T., Hall, E. D., Marion, D. W., Trudel, T., et al. (2008). Traumatic brain injury research priorities: The Conemaugh International Brain Injury Symposium. *Journal of Neurotrauma, 25*(10), 1135–1152. doi:10.1089/neu.2008.0599.