

# Diagnosis and Management of Acute Concussion

Meeryo C. Choe, MD<sup>1</sup> Christopher C. Giza, MD<sup>2</sup>

<sup>1</sup> Division of Pediatric Neurology, David Geffen School of Medicine at UCLA, Mattel Children's Hospital UCLA, Los Angeles, California

<sup>2</sup> Division of Pediatric Neurology and Department of Neurosurgery, UCLA Brain Injury Research Center, David Geffen School of Medicine at UCLA, Los Angeles, California

Address for correspondence Meeryo C. Choe, MD, Division of Pediatric Neurology, David Geffen School of Medicine at UCLA, Mattel Children's Hospital, UCLA, 22-474 MDCC, 10833 LeConte Avenue, Los Angeles, CA 90095-1752 (e-mail: mchoe@mednet.ucla.edu).

Semin Neurol 2015;35:29–41.

## Abstract

Mild traumatic brain injury (mTBI), or concussion, constitutes a significant percentage of the millions of TBIs sustained in the United States each year. Symptoms are typically short-lived, and may correlate to physiologic changes in the acute period after injury. There are many available tools that can be utilized on the sideline as well as in the clinical setting for assessment and diagnosis of concussion. It is important to use validated tests in conjunction with a thorough history and physical examination. Neurocognitive testing may be helpful in the subacute period. Management should begin with removal from risk if a concussion is suspected, and once diagnosis is made, education and reassurance should be provided. Once symptoms have resolved, a graded return-to-play protocol can be implemented with close supervision and observation for return of symptoms. Management should be tailored to the individual, and if symptoms are prolonged, further diagnostic evaluation may be necessary.

## Keywords

- ▶ mild traumatic brain injury
- ▶ concussion
- ▶ diagnosis
- ▶ return-to-play

Traumatic brain injury (TBI), a major cause of death and life-long disability, is a significant growing health problem. Approximately 75 to 80% of TBIs are mild in severity, resulting from closed head injury, sometimes referred to as concussion, and is especially prevalent in sports and among military personnel.<sup>1,2</sup> Between 1.6 and 3.8 million sport-related concussions are diagnosed each year, and recent studies have projected that 15 to 30% of those deployed in the conflicts in Afghanistan and Iraq (Operation Enduring Freedom/Operation Iraqi Freedom [OEF/OIF]) have sustained injuries to the head and neck region.<sup>3–6</sup> The majority of TBI occurs in males 15 to 24 years of age, reflecting those populations in which risk for injury is high.<sup>1</sup> Mild TBI (mTBI) accounts for over one million emergency room visits, with 40% of individuals suffering from long-term disability, thus making it a significant public health issue.<sup>7,8</sup> The Centers for Disease Control estimates that 5.3 million Americans are living with TBI-related disability.<sup>9</sup> Most patients recover completely from their mTBI, but up to 30% may continue to suffer symptoms long term with somatic, cognitive, and emotional issues including headaches, dizziness, memory difficulties, mood disorders, and anxiety.<sup>10,11</sup>

Traumatic brain injury is defined as “an injury to the head as a result of blunt trauma or acceleration or deceleration forces that result in one or more of the following conditions: any period of observed or self-reported: transient confusion, disorientation, or impaired consciousness; dysfunction of memory around the time of injury; or loss of consciousness lasting less than 30 minutes.”<sup>12</sup> Traumatic brain injury severity is based primarily on the duration of loss of consciousness, duration of posttraumatic amnesia, and the Glasgow Coma Scale (GCS) score at time of evaluation. Mild TBI is characterized by a GCS of 13 to 15, with loss of consciousness (LOC) less than 30 minutes and duration of posttraumatic amnesia less than 24 hours.<sup>13</sup> The incidence of mTBIs presenting to EDs has significantly increased, indicating the importance of understanding the diagnosis and management of this important growing problem.<sup>14,15</sup> mTBI and concussion are overlapping terms that describe TBI on the less severe end of the spectrum. Concussion, as defined by the 4<sup>th</sup> International Conference on Concussion in Sport in 2012, “is a brain injury and is defined as a complex pathophysiological process affecting the brain, induced by biomechanical forces.” The injury may result from

Issue Theme Traumatic Brain Injury;  
Guest Editor, Geoffrey Ling, MD, PhD,  
FAAN, FANA

Copyright © 2015 by Thieme Medical  
Publishers, Inc., 333 Seventh Avenue,  
New York, NY 10001, USA.  
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0035-1544243>.  
ISSN 0271-8235.

a direct blow, or may be “an ‘impulsive’ force transmitted to the head. Concussion typically results in the rapid onset of short-lived impairment of neurological function that resolves spontaneously...may result in neuropathological changes... and results in a graded set of clinical symptoms that may or may not involve loss of consciousness.” This definition also states that “no abnormality is seen on standard structural neuroimaging studies,” and “in some cases symptoms may be prolonged.”<sup>16</sup> For the purpose of this review, we will use the terms “mild TBI” and “concussion” interchangeably. However, there are some who consider these two terms to be different, showing that in children, better outcome is correlated with the term “concussion.”<sup>17</sup>

Specific populations requiring special consideration with regards to mTBI include athletes and military personnel. These groups sustain a high number of injuries that may involve the brain as well as other parts of the body. They also make up a significant proportion of those who suffer brain injuries in the United States. Sports-related injuries account for approximately one-fifth of the TBIs in the United States,<sup>15</sup> with 55% receiving outpatient care and 34% receiving no medical care.<sup>1,15</sup> Most sports-related TBIs fall into the mild or moderate category. Studies of deployed military forces to Iraq and Afghanistan estimate that 20% of have suffered a head injury, with those sustained in combat most often due to blast injury.<sup>18</sup> However, studies show that TBI sustained in the military are more likely due to other mechanisms such as motor vehicle accidents, falls, training, or sports and assaults.<sup>19</sup> The prevalence of those who have suffered a mTBI ranges from 4.2 to 23%.<sup>20</sup> Often, symptoms of TBI and posttraumatic stress disorder (PTSD) coexist in armed forces personnel. In both of these populations (athlete and military), there may be less willingness to report an injury, as an athlete may not want to be taken out of his or her sport, similar to a soldier wanting to remain on duty. Therefore, it becomes especially critical to have adequate diagnostic tools to accurately determine the occurrence of mTBI in these groups.

## Pathophysiology

Symptoms after mild TBI may be attributable to pathophysiological changes that occur in the brain after injury. Acceleration–deceleration of the brain within the skull results in a stretch and strain upon the white matter and directly to cortical areas. Our knowledge of mTBI pathophysiology derives primarily from studies in animal models, as well as from clinical studies of severe human TBI using invasive monitoring. Animal models characterizing pathological changes and functional correlates, particularly behavioral and cognitive impairments, include fluid percussion, controlled cortical impact, and weight drop injuries.<sup>21</sup> In addition, there are newer models of repeat mTBI/concussion that focus on functional impairment with minimal histological injury.<sup>22–24</sup> After impact occurs, a cascade of intracellular and extracellular processes occurs including neurotransmitter release, alteration in cerebral blood flow, mitochondrial dysfunction, and free-radical formation. Neuronal cell membrane disruptions and axonal stretching occur, with resulting indiscriminate movement of

ions and neurotransmitters across the disturbed membrane.<sup>25</sup> Glutamate is released from presynaptic terminals and activates N-methyl-D-aspartate (NMDA) receptors, further exacerbating these ion shifts. Potassium is released extracellularly,<sup>26,27</sup> and the Na<sup>+</sup>/K ATP-dependent pump attempts to re-establish ionic equilibrium with resulting depletion of energy stores. Extracellular potassium increases lead to further neuronal depolarization.<sup>28,29</sup> Calcium accumulation occurs intracellularly, leading to mitochondrial calcium overload with resulting mitochondrial dysfunction and oxidative stress.<sup>30</sup> This calcium accumulation has been shown in animal models to correlate with persistent cognitive deficits as detected on Morris water maze testing.<sup>31,32</sup>

In addition to the ionic and neurotransmitter dysregulation that occurs, changes in cerebral glucose metabolism have also been shown both in animal and human studies. There is an initial rapid increase in glucose uptake, which is followed by prolonged glucose metabolic depression.<sup>33</sup> This increase may be secondary to cellular energy needs to restore ionic balance.<sup>34–36</sup> Increased cerebral glucose metabolism is followed by a period of decreased glucose metabolism, and is proportional in magnitude and duration to injury severity in rat models<sup>37</sup> as well as in TBI patients.<sup>38,39</sup> This glucose metabolic depression may be due to multiple reasons, including decreased cerebral blood flow, reduced demand, and impaired glucose transporter function. Animal studies have shown a decrease in cerebral blood flow during the acute phase after injury, with a resultant mismatch between needs and glucose availability.<sup>40</sup> Additionally, there may be decreased expression of the GLUT1 transporter.<sup>41</sup>

Increased free-radical production may occur after injury, which causes free-radical scavengers to be overwhelmed, leading to oxidative damage.<sup>42,43</sup> This free-radical production may be the result of intracellular calcium accumulation that activates free-radical-producing enzymes concomitantly with decreased availability of reducing equivalents. The combination of increased intracellular calcium and reactive oxygen species leads to mitochondrial dysfunction, which in turn reduces energy production, thus potentially initiating cell death through apoptotic and necrotic pathways.<sup>44–46</sup>

In addition to the chemical changes occurring throughout the brain, stretching and shearing of axons throughout the white matter leads to diffuse axonal injury (DAI), particularly in the brainstem, corpus callosum, and frontal lobes.<sup>47,48</sup> Cell membrane permeability, membrane potential, and cytoskeletal disruption occurs, with axonal transport disturbance. Buildup of transport organelles leads to edema, and secondary axotomy may occur leading to “retraction balls.” However, there is some debate as to whether DAI may or may not be the primary mechanism of symptomatology behind postconcussive symptoms.<sup>49</sup>

More recently, use of multimodal magnetic resonance imaging (MRI) techniques such as 1H-magnetic resonance spectroscopy (MRS) has furthered the understanding of metabolic changes that occur after mTBI. N-acetylaspartate (NAA) diminishes after mTBI, and may represent neuronal and/or mitochondrial dysfunction; however, its exact function is not completely understood.<sup>50–52</sup> MRS studies have

shown that this decrease in NAA can recover 30 days after injury.<sup>50</sup> However, the temporal range of decreased NAA has been shown to range from days to months to years after injury.<sup>50,53-57</sup> Interestingly, postconcussion reductions in NAA are exacerbated (greater reductions and longer duration—45 days) after repeated concussions.<sup>50</sup>

The pathophysiology of military-related TBI may be different than other TBI sustained from falls, blunt trauma, and sports-related concussions. In a retrospective study of inpatient admission from OIF, Bell et al found that of the 1,513 consultations made by the neurosurgery population, blast injury accounted for almost 60% of military-related TBI.<sup>58</sup> However, other estimates maintain that mTBI sustained in the military looks mechanically and demographically like sport-related concussion.<sup>19</sup> Many characteristics of the blast determine the resulting effects, including the distance from the blast, whether the blast occurred in an open or closed space, pressure waves that may be reflected off surrounding surfaces, and characteristics of the improvised explosive device (IED).<sup>59</sup> Blast injury results from the transmitted acoustic wave through the brain (primary blast wave) and accompanying blast winds.<sup>60</sup> Vascular damage with hemorrhage and sometimes vasospasm may be triggered, which can lead to ischemia and further clinical deterioration.<sup>61-63</sup>

## Assessment and Diagnosis

Defining a concussion or mTBI is difficult due to lack of objective measurements on which to base a diagnosis. Typically, history, symptom report, and clinical assessment are used to make the diagnosis. Ancillary testing may include imaging and cognitive or neuropsychological assessment. As defined above, TBI is an injury to the brain that results from either a direct blow or transmitted force to the brain that results in neurologic deficits. In terms of diagnosing a mTBI, these are injuries that result in less than 30 minutes of LOC, are associated with less than 24 hours of posttraumatic amnesia, and have a GCS at the time of initial evaluation of 13 to 15. One less clear consideration is whether intracranial injury should be taken into account when characterizing a TBI as mild. Studies have shown that those with complicated mild TBI have different outcomes from those with uncomplicated mTBI. However, defining complicated mild injuries is challenging, as early studies suggest that complicated mTBI should be defined as that with space-occupying lesions. More recently, researchers have suggested that complicated mTBI should be defined strictly as those injuries that have intracranial findings and/or a depressed skull fracture.<sup>64-66</sup> Even more vagueness occurs in defining intracranial injury. Furthermore, finding the intracranial injury requires imaging, which may include computed tomography (CT) and/or MRI, and there is no consensus as to which should be required to characterize the intracranial findings.<sup>67,68</sup> Early studies outlining outcome after mTBI characterize complicated mTBI as those with GCS of 13 to 15 and a space-occupying lesion, including contusion, hemorrhage, or hematomas.<sup>69</sup> Those patients as defined by CT with a space-occupying lesion showed greater cognitive deficit beyond one month after injury.<sup>69</sup> The Transforming Research and Clinical

Knowledge in Traumatic Brain Injury (TRACK-TBI) study has focused on defining patients by utilizing a Marshall CT classification of 5 or 6 (indicative of complicated mTBI with pathological head CT findings) and determining long-term outcome.<sup>70</sup> Other recent studies also show that not only is long-term outcome worse with a complicated mTBI compared with uncomplicated mTBI, but that this outcome may be related to cognitive reserve.<sup>68</sup>

## Concussion Assessment Tools

The Sports Concussion Assessment Tool (SCAT) is based on expert consensus from those attending the serial Concussion in Sport Conferences (CISs) as an acute measure to assess sport-related concussion on the sideline, or for other evaluation in the immediate period after injury.<sup>16,71-73</sup> It has been revised 3 times based on expert consensus and scientific evidence.<sup>16,72-74</sup> The Third CIS Conference produced a PocketSCAT2 that was designed as a brief sideline tool, whereas the SCAT2 is a longer version, intended for tracking recovery serially.<sup>16</sup> The Fourth CIS Conference produced the most recent version of the SCAT3 and differs in scoring (omission of 100-point scoring and scoring of symptoms and balance) and the addition of tandem gait in addition to, or in place of the Modified Balance Error Scoring System (M-BESS).<sup>73,74</sup> Components of the SCAT3 include a symptom questionnaire (Graded Symptom Checklist [GSC]), cognitive assessment (Standardized Assessment of Concussion [SAC]), rating of physical signs, a coordination exam, and a balance examination (M-BESS), as described in more detail below.<sup>73</sup> These components have been shown to be reliable, sensitive, and specific.<sup>74</sup> In addition to an updated SCAT3, the Fourth CIS Conference produced a Child-SCAT3 designed for children between 5 to 12 years of age.<sup>73</sup> However practical, the Child-SCAT3 is not yet validated.

The Military Acute Concussion Evaluation (MACE) is a correlative screening test used in the military setting.<sup>75</sup> It is comprised of historical and objective sections, and has been used to some extent to make return-to-duty decisions.<sup>76</sup> The historical portion essentially covers the data regarding the injury and any acute signs and symptoms including the presence of amnesia and LOC, as well as the presence or absence of nine symptoms. The symptom score alone has been shown to have poor accuracy; furthermore, it does not improve diagnosis when used with the SAC.<sup>77</sup> The objective portion is made up of the Standardized Assessment of Concussion (SAC), which is described below. There are several limitations to the MACE, including inconsistent obtainment of baseline evaluations in service members, and therefore reliance on an absolute score of < 24 to diagnose a concussion.<sup>78</sup> A 2010 study showed that the MACE lacked sensitivity and specificity, and therefore was not valid if administered more than 12 hours after injury.<sup>78</sup>

## Maddocks Sideline Questions

One component of the SCAT3 designed to quickly assess attention and memory is the Maddocks test.<sup>79</sup> Prior to the development of this test, concussion diagnosis relied on the

length of LOC and posttraumatic amnesia to determine severity, failing to acknowledge the large number of sport-related concussions that do not result in LOC. Maddocks proposed that traditional orientation questions were not sensitive enough to diagnose the milder injuries sustained in sports, and suggested that game-oriented questions may be more appropriate.<sup>79,80</sup> In a study of 28 players diagnosed as having suffered a concussion, he determined that questions specific to the game/sport, such as “Which quarter?,” “Last goal?” “Who was the opponent last week?” may be more sensitive than traditional orientation questions for the diagnosis of mild concussion sustained in sport.<sup>79</sup>

### Graded Symptom Checklist/ Postconcussion Symptom Scores

Symptoms after a concussion may vary, and measurement depends on self-report, making accurate quantification difficult. These symptoms typically resolve in the first week after injury for the majority who sustain mTBI.<sup>81–83</sup> The Graded Symptom Checklist (GSC) on the SCAT versions is a subjective measure that can be documented for an individual, useful for comparing pre- and postinjury scores as well as monitoring symptoms throughout recovery.<sup>73</sup> The symptom score is made up of a 22-item scale using a 7-point Likert scale. The scale has been shown to be reliable and valid, and may be used in the acute assessment as well as serially during recovery to assess improvement.<sup>84–86</sup> On the Child-SCAT3, there are both self and parental reports of symptoms.<sup>73</sup> However, these have not yet been validated.

### Standardized Assessment of Concussion

The Standardized Assessment of Concussion (SAC) was developed for use immediately after an injury, and has been validated for evaluation in a sport-related concussion context.<sup>87</sup> Studies show sensitivity in the first 48 hours following a concussion.<sup>82,88</sup> The validation studies rely on changes from baseline rather than one-time scores to diagnose impairment after injury.<sup>89–91</sup> When used shortly after an event, the SAC has good sensitivity and specificity for distinguishing cognitive problems after concussion (sensitivity 80–94%, specificity 76–91%).<sup>89,90</sup> Kennedy et al showed that the SAC was only useful in the first 6 hours after injury, and in a military population did not predict outcome.<sup>92</sup> The SAC is a useful screening tool for detecting mTBI-related cognitive impairment, and responses to the psychologically grouped symptoms may even help to predict persistent postconcussive symptoms.<sup>77</sup>

### Balance Error Scoring System

Measurement of postural stability using brief sideline assessment tools has been one of the diagnostic methods proposed for objective evaluation of mild head injury. Maintenance of balance requires multiple sensory inputs and outputs to the muscles. A clinical, practical, and cost-effective method, the BESS, has been developed as a standardized, quick sideline measurement of postural stability. The patient holds three different stances (double leg, single leg, tandem) on a firm surface and a medium density foam pad, each for 20 seconds with hands on hips and eyes

closed. Errors are counted and summed to a maximum error score of 10 per trial.<sup>93</sup> The SCAT3 relies on a M-BESS, only assessing an individual's balance by evaluating the three stances on the flat ground.<sup>73</sup> The full BESS (including foam pad) has good specificity (91%), but only moderate sensitivity (34–64%) for diagnosis of concussion.<sup>89,94</sup> The M-BESS however, has no published data documenting its sensitivity. Luoto et al found that in an adult sample of patients with mTBI, their M-BESS scores did not differ significantly from controls.<sup>77</sup> Additionally, balance has been suggested to recover sooner than other deficits that may persist longer after concussion.<sup>77,82</sup> Balance testing by NeuroCom International Smart Balance Master System or sensory organization test (SOT) utilizes a force plate to measure stability and sway in multiple sensory conditions that are increasingly more difficult. A score is calculated for each trial, and a composite score determines overall postural stability.<sup>95</sup> Correlations between the BESS and force platform sway or SOT measures with good intertester reliability have been shown in controls, and differences between acutely injured and controls have also been demonstrated.<sup>96,97</sup> However, some issues include interrater reliability, environmental effects such as noise or anxiety, and orthopedic injuries resulting in functional ankle or lower limb instability.<sup>98–102</sup> In addition, there appears to be a practice or learning effect in studies in which subjects were tested repeatedly over short periods.<sup>103</sup>

### Reaction Time

Impaired reaction time has been shown to be one of the most sensitive indicators of persistent deficit after injury. Reaction time has traditionally been measured by computerized testing (RTcomp), usually assessed by pushing a key in response to a prompt. Another method that has been developed to objectively evaluate reaction time of individuals on the sideline, and without a computer, is the clinical reaction time test (RTclin).<sup>104–106</sup> Considerable research has shown that reaction time is prolonged immediately after injury, and improves gradually until returning to baseline.<sup>104</sup> Reaction time may even persist beyond resolution of symptoms, thus making it a useful tool in objectively assessing recovery to be used in conjunction with a patient's self-reported symptoms. The pilot study using the clinical RT tool/stick showed a positive correlation between the RTclin and RTcomp in athletes whose effort was deemed valid by the built-in integrity check of the CogState/Axon Sport computerized test. Additionally, the data showed less variability in the RTclin test, suggesting that motivation may be increased in this assessment as compared with computerized testing.<sup>105</sup> In follow-up studies, Eckner et al demonstrated consistent results across seasons as well as correlative deficits in RTclin and RTcomp in athletes after concussion.<sup>104,107</sup> Recent studies have shown practice effect with improvement in time in similar clinical reaction time tests, such as the ruler-drop test.<sup>108</sup>

### King-Devick Test

Like the SCAT versions, the King-Devick test (K-D) was proposed as a sideline tool to detect sport-related concussion.

The K-D is a brief (< 1 minute) test requiring saccadic eye movements on a fixed target to read a series of numbers on three test cards. Numerous processes are required for oculomotor function, including sensory and motor components, as well as cognitive processes such as concentration, attention, and spatial memory.<sup>109,110</sup> In a test of professional ice hockey players, Galetta et al found that K-D scores correlated with lower scores of immediate memory on the SAC at preseason baseline.<sup>111</sup> They proposed that this may be due to function specifically in the dorsolateral prefrontal cortex as this brain region plays a role in saccadic eye movement control and working memory. They also found increased time (worse scores) in two athletes who had sustained concussion, consistent with findings in prior studies showing increased K-D time scores after concussion in contact and collision sport athletes.<sup>112–114</sup> Similar to other available tests, athletes showed statistically significant improvement between pre- and postseason testing.<sup>113</sup> But the clinical significance of a 2.8-second difference is not clear.<sup>113</sup> Despite studies correlating K-D results to the SAC and MACE, no longitudinal studies assessing validity or generalizability have been performed.<sup>112</sup>

### Neuropsychological Testing

Neuropsychological testing can be divided into traditional paper-and-pencil testing with a neuropsychologist and computerized cognitive tests. These tests were designed to identify cognitive impairments that frequently occur after injury, and may be able to identify deficits in those individuals who are reporting an absence of symptoms.<sup>115–118</sup> Traditional paper-and-pencil neuropsychological testing administered by a neuropsychologist may be used in the postinjury period to assess cognitive issues that frequently plague individuals after TBI. Typically, referrals for neuropsychological testing are made when a patient reports particular commonly experienced cognitive issues, such as problems with memory, concentration, and attention, but may also be used when mood symptoms are prominent. Pencil-and-paper testing may be more comprehensive, and as a dynamic testing situation, may test additional domains with the ability to distinguish between effects of a concussion and premorbid conditions.<sup>73,118,119</sup>

However, because formal neuropsychological testing is not always practical, particularly in the athletic and military settings, computerized neurocognitive testing has been utilized frequently. As paper-and-pencil testing requires accessibility to a neuropsychologist, a quiet testing environment, and a significant amount of time, this type of cognitive testing may not be readily available in many arenas when evaluating a head injury. Computerized test batteries are objective methods for testing large groups, are generally brief, and can be used in follow-up for tracking recovery. In these populations, computerized neurocognitive assessments may be administered at baseline so that in the case of injury, there is a standard to which postinjury tests can be compared. With athletes as well as military personnel, return to baseline determinations are particularly important, as these individuals are at a higher risk for a repeat injury, and additionally may

be at risk for a more catastrophic injury.<sup>120</sup> The advantages over traditional neuropsychological testing include ease of administration (time of testing, decreases need for additional personnel), alternate test forms, and reduction of practice effects (alternate forms, randomized test stimuli). However, a single baseline neurocognitive test may not provide an accurate representation of an individual's cognitive status. More recently, there is growing evidence that neuropsychological testing can also be used effectively in the absence of a baseline result.<sup>115,121</sup>

There are several commonly used computerized neurocognitive tests available for use. Each test utilizes multiple tasks that when analyzed, comprise several different metrics of cognitive ability. These include but are not limited to the Immediate Post Concussion Assessment and Cognitive Testing (ImPACT), CogState/Axon, CNS Vital Signs, and Automated Neuropsychological Assessment Metrics (ANAM). The most commonly administered test is the ImPACT, which evaluates different cognitive modalities across a variety of tests. Multiple studies have shown good sensitivity and specificity in athletes, 81.9 to 91.7% and 69.1 to 89.4%, respectively.<sup>85,122–124</sup> However, multiple studies assessing reliability over a range of populations have yielded mixed results over varying time intervals, ranging from 1 month to 2 years.<sup>123,125–127</sup> A more recent study has suggested that this may be attributable to different versions of the test used (i.e., desktop vs. online). However, results may be difficult to interpret when an inpatient baseline comparison is not available. There is normative data established for some of these tests.<sup>115,128–133</sup> In a recent study using the CogState/Axon test that compared the sensitivity and specificity of baseline and normative methods of comparison to determine concussion in elite adult, male athletes, it was found that the baseline method had a higher sensitivity and specificity than normative methods.<sup>132</sup>

In 2008, Congress mandated that U.S. military service members have pre- and postdeployment computerized cognitive testing due to increasing awareness and concern for the risk of brain injury during deployment. The most commonly used test used in the military setting is the ANAM, whose normative data has been published.<sup>134</sup> Roebuck-Spencer et al determined that the determination of atypical individuals based on normative data from the ANAM4 was inconsistent between pre- and postdeployment tests within the same individual. Furthermore, they saw that a large number of those classified as atypical were no different in postdeployment from their baseline, suggesting that using normative standards falsely identified these individuals as atypical.<sup>135</sup>

However, due to ease of administration, some athletic programs are solely utilizing computerized neurocognitive tests for making decisions regarding return to activity. All current evidence- and consensus-based sports concussion recommendations advise against having a single test to diagnose or manage concussion, and that these tests should be used in conjunction with other evaluation modalities to make diagnostic and management decisions. Additional issues with computerized neurocognitive testing include premorbid learning disabilities that are not discernable on

computerized testing, underreporting of prior concussions, language issues, administration of testing in a suboptimal environment (including an unsupervised condition), and appropriateness of the test for the age of the injured individual.<sup>136</sup> Although many of these concerns are addressed by comparing baseline and postinjury assessments within the same individual, this likely limits the use of computerized testing for assessment solely after injury, as a single administration postinjury may not be sufficient as an independent diagnostic tool. Other factors may play a role in performance on the exam, particularly relevant in the athlete and military populations, such as dehydration, motivation, fatigue, and other physical factors.<sup>137,138</sup> Although one study has shown no difference in dehydration in ANAM scores,<sup>137</sup> another study has shown that performance suffers when individuals have urinary urgency on the CogState/Axon test.<sup>139</sup> Hutchison et al found that acutely after injury, collegiate athletes had cognitive impairment on the ANAM test battery with either orthopedic injury or concussion.<sup>140</sup> Additionally, environmental factors, such as testing conditions and time of day, can also influence performance.<sup>141</sup> Evidence of practice effects has led some groups to recommend repeat baseline testing to minimize the effect of learning.<sup>142–145</sup> However, other groups have shown no stability in test-retest reliability in several computerized neurocognitive tests.<sup>123</sup> An additional difficulty in utilizing computerized testing is that some individuals may perform perfectly, suggesting a ceiling effect, which limits the ability of the test to detect minor changes, especially in those who perform at the top.<sup>146</sup> Similarly, a floor effect may also limit the usefulness of a test for determining changes in an individual who already performs poorly at baseline.<sup>142</sup>

### Imaging

Use of computed tomography (CT) to evaluate sports concussions specifically is only sparsely reported in the literature; however, multiple studies examining CT use for mTBI presenting in the emergency department (ED) have been conducted.<sup>147–151</sup> Computed tomography has been historically used as the standard of care for assessment of TBI in ED settings, but radiation exposure may present its own risks, particularly in children.<sup>152,153</sup> Jagoda et al recommended that noncontrast head CT should be obtained in an adult with TBI if LOC or posttraumatic amnesia (PTA) was present with headache or vomiting, intoxication, short-term memory deficits, posttraumatic seizure, GCS < 15, a focal neurologic deficit, coagulopathy, supraclavicular trauma or age > 60 years.<sup>147</sup> The Pediatric Emergency Care Applied Research Network (PECARN) proposed validated clinical prediction rules for clinically important TBI for children younger than 2 years and older than or equal to 2 years of age.<sup>148</sup> They identified six clinical predictors for each group. For those in the younger group, the predictors of intermediate risk for clinically important TBI are nonfrontal scalp hematoma, LOC  $\geq$  5 seconds, severe mechanism of injury, or abnormal behavior per parent. Higher risk predictors are altered mental status or palpable skull fracture. Predictors of intermediate risk for those 2 years old or older include any LOC, vomiting, severe

injury mechanism, or severe headache. Predictors of higher risk are altered mental status or clinical evidence of basilar skull fracture. The PECARN group categorized those at lowest risk in either group as those who did not have any of the clinical predictors.<sup>148</sup> In a follow-up study, they suggest that those with isolated severe injury mechanisms without any other risk predictors may be observed before deciding if CT is needed.<sup>149,151</sup> Validation of these prediction rules was recently published in a cohort of children from two EDs.<sup>150</sup>

Magnetic resonance imaging (MRI) has been suggested to be useful in determining outcome after injury. Previous studies using CT showed a correlation between intracranial hemorrhage and long-term deficits.<sup>154,155</sup> Magnetic resonance imaging is more sensitive for elucidating small, focal intracranial lesions, and thus may be more sensitive in determining those individuals at risk for prolonged recovery. The TRACK-TBI group studied mTBI patients presenting to the ED with CT and MRI, and found the presence of intracranial findings (cortical contusion or four or more microhemorrhages on MRI) predicted 3-month outcome, specifically for determining which patients may be those to develop persistent dysfunction.<sup>156</sup> Using the Extended Glasgow Outcome Scale (GOS-E) at 3 months postinjury to grade outcome, they determined that using MRI improves outcome prediction. Additionally, in a later study, Yuh et al determined that diffusion tensor imaging (DTI) findings could predict outcome at the 3- and 6-month postinjury time point. Specifically, they found that reduced fractional anisotropy (FA) in at least one region of interest (ROI) predicted worse Extended Glasgow Outcome Scale (GOS-E) scores at both time points, and MRI was better than other predictors at determining outcome at 3 and 6 months.<sup>157,158</sup>

### Management

For those individuals at higher risk of injury, such as those playing contact/collision sports or military service members, it is critical to have education regarding concussion risks as well as signs and symptoms of a concussion so they may remove themselves from further risk if a suspicious head injury is sustained. Education may be provided by a licensed health care professional, trained in concussion evaluation and management.<sup>94</sup>

The initial step in concussion management once a head injury occurs is removal from risk for evaluation and management according to the diagnosis. In the case of the athlete, this means he or she should be evaluated on the sideline, and if concussion is diagnosed, then he or she must be removed from the game or practice for treatment and recovery. In the military setting, this may be more difficult, as in War Theater, extraction of the military service member with suspected TBI may not be possible immediately but should be done as quickly and safely as possible. In either sports or the military, full assessment should be performed before he or she is allowed to return-to-play or duty. This is a critical step, as it is necessary to protect the individual from additional injury. An individual who sustains a concussion may demonstrate a slower reaction time, impaired balance, worsened visual

tracking, and cognitive difficulties, which would increase the risk for further injury. Published studies suggest a prior concussion increases the risk for a subsequent concussion by three- to sixfold.<sup>159-161</sup>

At the collegiate level, the National Collegiate Athletic Association (NCAA) has more recently promoted increased brain health and safety, specifically adopting a concussion policy and legislation in 2010.<sup>162</sup> Each stakeholder school is mandated to have a concussion management plan, including education, removal from play if a concussion is suspected, no same-day return if a concussion is suspected, and medical clearance prior to return-to-play determined by a physician or designee of the physician.<sup>162</sup> There are more than 450,000 athletes affected by this.<sup>163</sup> Using a survey of coaches, clinicians, and administrators evaluating the implementation and effectiveness of the policy, Baugh et al found institutional concussion management plans were in place at 92.7% of the schools, with team physicians and/or athletic trainers primarily having final responsibility for return-to-play decisions.<sup>164</sup> However, in the younger age groups, where the majority of athletes participate, there is no unifying policy regarding concussion education and management, often due either to a lack of a national organizing body, or to multiple different youth sports organizations with differing policies.

Once immediate risk is eliminated, physical and cognitive rest until acute symptoms have resolved is typically recommended.<sup>73,94,165</sup> However, the evidence for this protocol is limited, and in particular, there is no consensus period for which rest should be prescribed, and the exact recommendations of "rest" are not clear.<sup>166-169</sup>

When discussing the recovery process, reassurance and education of the individual must be provided. This brief psychological intervention has been termed *cognitive restructuring*; in a pediatric setting it is akin to anticipatory guidance. Cognitive restructuring has been shown to be effective in mTBI as a preventative measure for the development of persistent symptoms, and specifically may be helpful in sleep issues and mood disorders as suggested by studies in uninjured youth.<sup>170-172</sup> This type of anticipatory guidance may also involve a reattribution of symptoms, which may decrease the risk of developing chronic postconcussion syndrome.<sup>94</sup>

For return to sports, the CIS conferences have developed a consensus-based graded return-to-play protocol, designed to allow athletes to return to physical activity in a stepwise fashion.<sup>16,73</sup> Though ideally one should be asymptomatic before returning to activity, in cases of chronic symptoms, sometimes returning to noncontact, low-risk physical activity can be beneficial. But he or she should not return to contact-risk until a licensed health care professional has determined that the concussion has resolved. A special consideration in the pediatric and collegiate populations is return-to-learn prior to return-to-play. With these student-athletes, the authors recommend that he or she should be back to full schoolwork without accommodations before returning to full physical activity. These individuals may proceed through returning to school slowly with accommodations as needed, until they are able to participate fully in school. As younger athletes are slower to reach symptom resolution, the

return-to-play protocol should be implemented more conservatively.<sup>94,173,174</sup> In addition, because validation of frequently used concussion assessment tools is primarily in the adult population, these tests should be used cautiously in the pediatric population for assessment of recovery after concussion, and there is an urgent need for better validated concussion assessment tools for use in the youth population.

The military has adopted strategies for return to duty based on sport-related return-to-play protocols for active-duty service members, with acute management demanding at least a 24-hour rest period and off-duty until asymptomatic.<sup>75</sup> Additionally, with two documented mTBIs in one year, the injured personnel should remain off active duty for at least 7 days after symptom resolution. After three documented mTBIs within one year, he or she must undergo comprehensive evaluation including neurologic exam, neuroimaging, and neuropsychological and functional assessments if necessary.<sup>75</sup>

Eighty-ninety percent of individuals have symptoms that resolve in the acute period (within 3 weeks) and are self-limited. Frequently reported categories of symptoms include somatic symptoms (such as headache, nausea, and dizziness), cognitive symptoms such as (decreased attention/concentration, difficulty with memory), mood symptoms (such as sadness, irritability, nervousness/anxiety), and problems with sleep. Initial management should include rest from both cognitive and physical activities acutely, and a gradual increase in these activities as tolerated. Management of acute headache may be achieved with traditional over-the-counter remedies such as acetaminophen, ibuprofen, or naproxen. Typically, more-aggressive management is not needed acutely. In some cases, headaches may persist and require further interventions depending upon the headache diagnosis (migraine, tension, medication-overuse, cervicogenic, etc.). Although no pharmacological intervention for the treatment of postconcussive symptoms is approved by the U.S. Food and Drug Administration, treatment of specific, prolonged symptoms may be approached as if in isolation.<sup>73,94,165</sup> Acute management of headaches with migrainous features may include triptans, and should the headache be frequent and persist past 3 to 4 weeks, treatment with prophylactic interventions such as topiramate, magnesium, tricyclic antidepressants (amitriptyline, nortriptyline), or  $\beta$ -blockers may be necessary. Similarly, treatment of other concurrent postconcussive symptoms in the subacute period may include selective serotonin reuptake inhibitors or other anti-anxiety or antidepressants for mood disorders, melatonin for sleep, and psychotherapy or cognitive-behavioral therapy for various cognitive or behavioral issues.

Though rest is recommended initially, prolonged rest may in fact be detrimental. Therefore, if symptoms are persistent, athletes may benefit from return to some activity without contact risk while waiting for complete symptom resolution. Those who are isolated from their teams or not undertaking any cardiovascular activity may experience increased depression and anxiety, which can cloud the evaluation of recovery of postconcussive symptoms. Low-level, monitored activity may be beneficial even in those athletes who continue to be

symptomatic, as suggested by studies in individuals with migraines and mood disorders.<sup>175–177</sup> Leddy et al suggested that controlled exercise training at a subsymptom threshold level improved postconcussive symptoms compared with no treatment in a small case series.<sup>178</sup> Furthermore, they demonstrated functional MRI activation similar to controls in those patients with postconcussive symptoms who received exercise treatment.<sup>179</sup>

In the military population, concurrent mTBI and PTSD occurs in almost a third of all those with probable concussion.<sup>180</sup> Posttraumatic stress disorder is a relatively common problem among service members, with a conservative prevalence of 16,000 cases in deployed personnel in 2011.<sup>181</sup> However, this number is likely a significant underestimate due to the restrictive terms of diagnosis.<sup>182</sup> The association is greater in those service members who experienced blast injury and did not have a concurrent injury.<sup>183</sup> In this population, postconcussive symptoms may easily be confused with other psychiatric conditions such as PTSD, mood disorders, and chronic pain. Furthermore, these types of symptoms are reported even by service members who were not injured in Theater.<sup>184</sup> Addressing PTSD is a critical piece of improving recovery after injury in this population, as studies suggest that PTSD and postconcussive symptoms are associated with poorer prognosis.<sup>182</sup> Treating psychiatric comorbidities is particularly important given that the suicide rates have been rising over the last decade, and those with TBI are at an increased risk of both suicidal ideation and suicidal attempts/death.<sup>76,185–187</sup>

For those individuals who have sustained multiple concussions, retirement from the offending activity (contact sport, military) may be recommended. When an individual reports chronic cognitive or behavioral issues, he or she may be referred for formal neuropsychological assessment. Retirement should be definitively recommended for those demonstrating dementia/degeneration, permanent or lasting neurocognitive impairment, or intractable pain. Additionally, those individuals who sustain injuries at a decreased interval between injuries, who have longer recovery after subsequent concussions, or who demonstrate a lower impact threshold for concussion may be counseled regarding the risk of further injury in terms of persistence of symptoms.<sup>94</sup>

## Summary

Accurate concussion diagnosis and appropriate management are critical, as prior concussions predispose athletes to sustaining an additional concussion. Furthermore, repeat concussion may result in worse long-term outcomes, although the extent remains unclear. There are numerous diagnostic tools available to clinicians to aid in assessing individuals with a suspected concussion. On the sideline, the Maddocks questions are often used in sports settings; the MACE serves as a screening tool in the military. In the acute/subacute setting, preferably in a quieter setting (locker room, clinic, etc.) the SCAT3 may be used to assess symptoms, cognition, and balance, and takes 10 to 12 minutes. Computerized or traditional cognitive testing may have a role subacutely, or when

attempting to determine return to duty/play as symptoms resolve, but require proper testing conditions and take more time (up to 20–30 minutes). Emerging tools include the clinical reaction time stick and the King-Devick test. Both are quick and relatively inexpensive, with varying specificity and sensitivity, but may play an increasing role, particularly in screening for acute concussion. Many more complex tools are worthy of continued research investigation, but are not yet ready for prime-time clinical usage, like visual tracking devices, advanced neuroimaging, or electrophysiological monitoring. Undoubtedly, some of these will be added to the concussion assessment armamentarium in the future. No single tool is sufficient to diagnose brain injury, and evaluation must include a thorough history, including symptom report, and neurologic examination in addition to validated adjunctive testing for balance, reaction time, visuomotor skills, and cognitive assessment.

Clinical management starts with identification of suspected concussion. In those scenarios, the individual should be removed from contact risk. For athletes, this means removal from play without return the same day, and formal evaluation by an experienced health care provider. For military personnel, this removal from risk is more problematic, but should be attempted when possible. Experienced clinical personnel should use the above tools to determine if a concussion occurred—conditions like migraine, anxiety, dehydration, hyperthermia, and others may mimic concussion symptoms and need to be treated differently. Once a concussion is diagnosed, education, reassurance, and cognitive restructuring should be implemented, as well as continued protection from contact risk. Clinical symptoms and neurologic function should be monitored and activity gradually increased as recovery ensues. Medications that mask symptoms should be weaned. Careful assessment of symptoms, cognition, balance, reaction time, and neurologic function are important to determine full recovery and eventual return to full activity and potential contact risk. Most return to play/duty protocols use a stepwise plan, with careful observation for symptoms or neurologic exacerbation at each step before advancing. For individuals who are having a prolonged recovery, further investigation and diagnostic testing may be needed to determine other etiologies and modify the treatment plan. Overall, management of concussion/mTBI is individualized to the specific patient. Multidisciplinary teams are optimal, particularly for those patients with more complex or prolonged recovery.

## References

- 1 Thurman DJ, Alverson C, Dunn KA, Guerrero J, Sniezek JE. Traumatic brain injury in the United States: A public health perspective. *J Head Trauma Rehabil* 1999;14(6):602–615
- 2 Langlois JA, Rutland-Brown W, Thomas KE. Traumatic brain injury in the United States: emergency department visits, hospitalizations, and deaths. Atlanta, GA: Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2004
- 3 Langlois JA, Rutland-Brown W, Wald MM. The epidemiology and impact of traumatic brain injury: a brief overview. *J Head Trauma Rehabil* 2006;21(5):375–378



- 4 Montgomery SP, Swiecki CW, Shriver CD. The evaluation of casualties from Operation Iraqi Freedom on return to the continental United States from March to June 2003. *J Am Coll Surg* 2005;201(1):7-12, discussion 12-13
- 5 Owens BD, Kragh JF Jr, Wenke JC, Macaitis J, Wade CE, Holcomb JB. Combat wounds in operation Iraqi Freedom and operation Enduring Freedom. *J Trauma* 2008;64(2):295-299
- 6 Rigg JL, Mooney SR. Concussions and the military: issues specific to service members. *PM R* 2011;3(10, Suppl 2):S380-S386
- 7 Corrigan JD, Selassie AW, Orman JA. The epidemiology of traumatic brain injury. *J Head Trauma Rehabil* 2010;25(2):72-80
- 8 Faul M, Likang X, Wald MM, Coronado VG, et al. Traumatic brain injury in the United States: emergency department visits, hospitalizations and deaths 2002-2006. Atlanta, GA: Centers for Disease Control and Prevention; 2010
- 9 National Center for Injury Prevention and Control. Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem. Atlanta, GA: Centers for Disease Control and Prevention; 2003
- 10 Hessen E, Nestvold K, Anderson V. Neuropsychological function 23 years after mild traumatic brain injury: a comparison of outcome after paediatric and adult head injuries. *Brain Inj* 2007;21(9):963-979
- 11 Vanderploeg RD, Curtiss G, Luis CA, Salazar AM. Long-term morbidities following self-reported mild traumatic brain injury. *J Clin Exp Neuropsychol* 2007;29(6):585-598
- 12 Thurman DALverson C, Browne D, et al. Traumatic Brain Injury in the United States: A Report to Congress. Atlanta, GA: Centers for Disease Control and Prevention; 1999
- 13 Mild Traumatic Brain Injury Committee, American Congress of Rehabilitation Medicine, Head Injury Interdisciplinary Special Interest Group. Definition of mild traumatic brain injury. *J Head Trauma Rehabil* 1993;8:86-87
- 14 Guerrero JL, Thurman DJ, Sniezek JE. Emergency department visits associated with traumatic brain injury: United States, 1995-1996. *Brain Inj* 2000;14(2):181-186
- 15 Sosin DM, Sacks JJ, Webb KW. Pediatric head injuries and deaths from bicycling in the United States. *Pediatrics* 1996;98(5):868-870
- 16 McCrory P, Meeuwisse W, Johnston K, et al. Consensus Statement on Concussion in Sport: The 3rd International Conference on Concussion in Sport held in Zurich, November 2008. *Br J Sports Med* 2009;43(Suppl 1):i76-i90
- 17 Dematteo CA, Hanna SE, Mahoney WJ, et al. "My child doesn't have a brain injury, he only has a concussion". *Pediatrics* 2010;125(2):327-334
- 18 Tanielian TL, Jaycox LH, Eds. Invisible wounds of war: psychological and cognitive injuries, their consequences, and services to assist recovery. Santa Monica, CA: RAND Corporation; 2008
- 19 Warden D. Military TBI during the Iraq and Afghanistan wars. *J Head Trauma Rehabil* 2006;21(5):398-402
- 20 Galarneau MR, Woodruff SI, Dye JL, Mohrle CR, Wade AL. Traumatic brain injury during Operation Iraqi Freedom: findings from the United States Navy-Marine Corps Combat Trauma Registry. *J Neurosurg* 2008;108(5):950-957
- 21 Namjoshi DR, Good C, Cheng WH, et al. Towards clinical management of traumatic brain injury: a review of models and mechanisms from a biomechanical perspective. *Dis Model Mech* 2013;6(6):1325-1338
- 22 DeFord SM, Wilson MS, Rice AC, et al. Repeated mild brain injuries result in cognitive impairment in B6C3F1 mice. *J Neurotrauma* 2002;19(4):427-438
- 23 Prins ML, Hales A, Reger M, Giza CC, Hovda DA. Repeat traumatic brain injury in the juvenile rat is associated with increased axonal injury and cognitive impairments. *Dev Neurosci* 2010;32(5-6):510-518
- 24 Longhi L, Pagan F, Valeriani V, et al. Monitoring brain tissue oxygen tension in brain-injured patients reveals hypoxic episodes in normal-appearing and in peri-focal tissue. *Intensive Care Med* 2007;33(12):2136-2142
- 25 Farkas O, Lifshitz J, Povlishock JT. Mechanoporation induced by diffuse traumatic brain injury: an irreversible or reversible response to injury? *J Neurosci* 2006;26(12):3130-3140
- 26 Katayama Y, Becker DP, Tamura T, Hovda DA. Massive increases in extracellular potassium and the indiscriminate release of glutamate following concussive brain injury. *J Neurosurg* 1990;73(6):889-900
- 27 Kawamata T, Katayama Y, Hovda DA, Yoshino A, Becker DP. Administration of excitatory amino acid antagonists via microdialysis attenuates the increase in glucose utilization seen following concussive brain injury. *J Cereb Blood Flow Metab* 1992;12(1):12-24
- 28 Giza CC, Hovda DA. The neurometabolic cascade of concussion. *J Athl Train* 2001;36(3):228-235
- 29 Giza CC, Hovda DA. The new neurometabolic cascade of concussion. *Neurosurgery* 2014;75(Suppl 4):S24-S33
- 30 Peng TI, Jou MJ. Oxidative stress caused by mitochondrial calcium overload. *Ann N Y Acad Sci* 2010;1201:183-188
- 31 Deshpande LS, Sun DA, Sombati S, et al. Alterations in neuronal calcium levels are associated with cognitive deficits after traumatic brain injury. *Neurosci Lett* 2008;441(1):115-119
- 32 Sun DA, Deshpande LS, Sombati S, et al. Traumatic brain injury causes a long-lasting calcium (Ca<sup>2+</sup>)-plateau of elevated intracellular Ca levels and altered Ca<sup>2+</sup> homeostatic mechanisms in hippocampal neurons surviving brain injury. *Eur J Neurosci* 2008;27(7):1659-1672
- 33 Yoshino A, Hovda DA, Kawamata T, Katayama Y, Becker DP. Dynamic changes in local cerebral glucose utilization following cerebral concussion in rats: evidence of a hyper- and subsequent hypometabolic state. *Brain Res* 1991;561(1):106-119
- 34 Hovda DA, Villablanca JR, Chugani HT, Phelps ME. Cerebral metabolism following neonatal or adult hemineodecortication in cats: I. Effects on glucose metabolism using [<sup>14</sup>C]2-deoxy-D-glucose autoradiography. *J Cereb Blood Flow Metab* 1996;16(1):134-146
- 35 Hovda DA, Yoshino A, Kawamata T, Katayama Y, Becker DP. Diffuse prolonged depression of cerebral oxidative metabolism following concussive brain injury in the rat: a cytochrome oxidase histochemistry study. *Brain Res* 1991;567(1):1-10
- 36 Hovda DA, Yoshino A, Kawamata T, Katayama Y, Fineman I, Becker DP. The increase in local cerebral glucose utilization following fluid percussion brain injury is prevented with kynurenic acid and is associated with an increase in calcium. *Acta Neurochir Suppl (Wien)* 1990;51:331-333
- 37 Hovda DA, Fu K, Badie H, Samii A, Pinanong P, Becker DP. Administration of an omega-conopeptide one hour following traumatic brain injury reduces 45calcium accumulation. *Acta Neurochir Suppl (Wien)* 1994;60:521-523
- 38 Bergsneider M, Hovda DA, Lee SM, et al. Dissociation of cerebral glucose metabolism and level of consciousness during the period of metabolic depression following human traumatic brain injury. *J Neurotrauma* 2000;17(5):389-401
- 39 Bergsneider M, Hovda DA, Shalmon E, et al. Cerebral hyperglycolysis following severe traumatic brain injury in humans: a positron emission tomography study. *J Neurosurg* 1997;86(2):241-251
- 40 Grundl PD, Biagas KV, Kochanek PM, Schiding JK, Barmada MA, Nemoto EM. Early cerebrovascular response to head injury in immature and mature rats. *J Neurotrauma* 1994;11(2):135-148
- 41 Balabanov R, Goldman H, Murphy S, et al. Endothelial cell activation following moderate traumatic brain injury. *Neuro Res* 2001;23(2-3):175-182
- 42 O'Connell KM, Littleton-Kearney MT. The role of free radicals in traumatic brain injury. *Biol Res Nurs* 2013;15(3):253-263
- 43 Kerr ME, Bender CM, Monti EJ. An introduction to oxygen free radicals. *Heart Lung* 1996;25(3):200-209, quiz 210-211

- 44 Prins ML, Alexander D, Giza CC, Hovda DA. Repeated mild traumatic brain injury: mechanisms of cerebral vulnerability. *J Neurotrauma* 2013;30(1):30–38
- 45 Lewén A, Skoglösa Y, Clausen F, et al. Paradoxical increase in neuronal DNA fragmentation after neuroprotective free radical scavenger treatment in experimental traumatic brain injury. *J Cereb Blood Flow Metab* 2001;21(4):344–350
- 46 Robertson CL. Mitochondrial dysfunction contributes to cell death following traumatic brain injury in adult and immature animals. *J Bioenerg Biomembr* 2004;36(4):363–368
- 47 Ajao DO, Pop V, Kamper JE, et al. Traumatic brain injury in young rats leads to progressive behavioral deficits coincident with altered tissue properties in adulthood. *J Neurotrauma* 2012;29(11):2060–2074
- 48 Creed JA, DiLeonardi AM, Fox DP, Tessler AR, Raghupathi R. Concussive brain trauma in the mouse results in acute cognitive deficits and sustained impairment of axonal function. *J Neurotrauma* 2011;28(4):547–563
- 49 Signoretti S, Lazzarino G, Tavazzi B, Vagnozzi R. The pathophysiology of concussion. *PM R* 2011;3(10, Suppl 2):S359–S368
- 50 Vagnozzi R, Signoretti S, Tavazzi B, et al. Temporal window of metabolic brain vulnerability to concussion: a pilot 1H-magnetic resonance spectroscopic study in concussed athletes—part III. *Neurosurgery* 2008;62(6):1286–1295, discussion 1295–1296
- 51 Vagnozzi R, Tavazzi B, Signoretti S, et al. Temporal window of metabolic brain vulnerability to concussions: mitochondrial-related impairment—part I. *Neurosurgery* 2007;61(2):379–388, discussion 388–389
- 52 Vagnozzi R, Signoretti S, Tavazzi B, et al. Hypothesis of the postconcussive vulnerable brain: experimental evidence of its metabolic occurrence. *Neurosurgery* 2005;57(1):164–171, discussion 164–171
- 53 Govindaraju V, Gauger GE, Manley GT, Ebel A, Meeker M, Maudsley AA. Volumetric proton spectroscopic imaging of mild traumatic brain injury. *AJNR Am J Neuroradiol* 2004;25(5):730–737
- 54 Henry LC, Tremblay S, Boulanger Y, ElleMBERG D, Lassonde M. Neurometabolic changes in the acute phase after sports concussions correlate with symptom severity. *J Neurotrauma* 2010;27(1):65–76
- 55 Henry LC, Tremblay S, Leclerc S, et al. Metabolic changes in concussed American football players during the acute and chronic post-injury phases. *BMC Neurol* 2011;11:105
- 56 Garnett MR, Blamire AM, Corkill RG, Cadoux-Hudson TA, Rajagopalan B, Styles P. Early proton magnetic resonance spectroscopy in normal-appearing brain correlates with outcome in patients following traumatic brain injury. *Brain* 2000;123(Pt 10):2046–2054
- 57 Cecil KM, Hills EC, Sandel ME, et al. Proton magnetic resonance spectroscopy for detection of axonal injury in the splenium of the corpus callosum of brain-injured patients. *J Neurosurg* 1998;88(5):795–801
- 58 Bell RS, Vo AH, Neal CJ, et al. Military traumatic brain and spinal column injury: a 5-year study of the impact blast and other military grade weaponry on the central nervous system. *J Trauma* 2009;66(4, Suppl):S104–S111
- 59 Duckworth JL, Grimes J, Ling GS. Pathophysiology of battlefield associated traumatic brain injury. *Pathophysiology* 2013;20(1):23–30
- 60 Rosenfeld JV, McFarlane AC, Bragge P, Armonda RA, Grimes JB, Ling GS. Blast-related traumatic brain injury. *Lancet Neurol* 2013;12(9):882–893
- 61 Bauman RA, Ling G, Tong L, et al. An introductory characterization of a combat-casualty-care relevant swine model of closed head injury resulting from exposure to explosive blast. *J Neurotrauma* 2009;26(6):841–860
- 62 Ling G, Bandak F, Armonda R, Grant G, Ecklund J. Explosive blast neurotrauma. *J Neurotrauma* 2009;26(6):815–825
- 63 Armonda RA, Bell RS, Vo AH, et al. Wartime traumatic cerebral vasospasm: recent review of combat casualties. *Neurosurgery* 2006;59(6):1215–1225, discussion 1225
- 64 Lange RT, Iverson GL, Franzen MD. Neuropsychological functioning following complicated vs. uncomplicated mild traumatic brain injury. *Brain Inj* 2009;23(2):83–91
- 65 Williams DH, Levin HS, Eisenberg HM. Mild head injury classification. *Neurosurgery* 1990;27(3):422–428
- 66 Iverson GL. Complicated vs uncomplicated mild traumatic brain injury: acute neuropsychological outcome. *Brain Inj* 2006;20(13-14):1335–1344
- 67 Karver CL, Wade SL, Cassidy A, et al. Cognitive reserve as a moderator of responsiveness to an online problem-solving intervention for adolescents with complicated mild-to-severe traumatic brain injury. *Child Neuropsychol* 2014;20(3):343–357
- 68 Fay TB, Yeates KO, Taylor HG, et al. Cognitive reserve as a moderator of postconcussive symptoms in children with complicated and uncomplicated mild traumatic brain injury. *J Int Neuropsychol Soc* 2010;16(1):94–105
- 69 Borgaro SR, Prigatano GP, Kwasnica C, Rexer JL. Cognitive and affective sequelae in complicated and uncomplicated mild traumatic brain injury. *Brain Inj* 2003;17(3):189–198
- 70 Lingsma HF, Yue JK, Maas AI, et al. Outcome prediction after mild and complicated mild traumatic brain injury: external validation of existing models and identification of new predictors using the TRACK-TBI pilot study. *J Neurotrauma* 2014; Epub ahead of print
- 71 Aubry M, Cantu R, Dvorak J, et al; Concussion in Sport Group. Summary and agreement statement of the First International Conference on Concussion in Sport, Vienna 2001. Recommendations for the improvement of safety and health of athletes who may suffer concussive injuries. *Br J Sports Med* 2002;36(1):6–10
- 72 McCrory P, Johnston K, Meeuwisse W, et al. Summary and agreement statement of the 2nd International Conference on Concussion in Sport, Prague 2004. *Br J Sports Med* 2005;39(4):196–204
- 73 McCrory P, Meeuwisse WH, Aubry M, et al. Consensus statement on concussion in sport: the 4th International Conference on Concussion in Sport held in Zurich, November 2012. *Br J Sports Med* 2013;47(5):250–258
- 74 Guskiewicz KM, Register-Mihalik J, McCrory P, et al. Evidence-based approach to revising the SCAT2: introducing the SCAT3. *Br J Sports Med* 2013;47(5):289–293
- 75 United States Department of Defense. DTM-09-033: Policy Guidance for Management of Concussion/Mild Traumatic Brain Injury in the Deployed Setting. Washington, DC: United States Department of Defense; 2010
- 76 Office of the US Army Surgeon General. OTSG/MEDCOM Policy Memo 09-068: Optimal Use of Psychological/Neurological Assessment. Rockland, MD: Office of the US Army Surgeon General; 2009
- 77 Luoto TM, Silverberg ND, Kataja A, et al. Sport concussion assessment tool 2 in a civilian trauma sample with mild traumatic brain injury. *J Neurotrauma* 2014;31(8):728–738
- 78 Coldren RL, Kelly MP, Parish RV, Dretsch M, Russell ML. Evaluation of the Military Acute Concussion Evaluation for use in combat operations more than 12 hours after injury. *Mil Med* 2010;175(7):477–481
- 79 Maddocks DL, Dicker GD, Saling MM. The assessment of orientation following concussion in athletes. *Clin J Sport Med* 1995;5(1):32–35
- 80 Yarnell PR, Lynch S. The 'ding': amnesic states in football trauma. *Neurology* 1973;23(2):196–197
- 81 Guskiewicz KM, McCrea M, Marshall SW, et al. Cumulative effects associated with recurrent concussion in collegiate football players: the NCAA Concussion Study. *JAMA* 2003;290(19):2549–2555
- 82 McCrea M, Guskiewicz KM, Marshall SW, et al. Acute effects and recovery time following concussion in collegiate football players: the NCAA Concussion Study. *JAMA* 2003;290(19):2556–2563

- 83 Makdissi M, Darby D, Maruff P, Ugoni A, Brukner P, McCrory PR. Natural history of concussion in sport: markers of severity and implications for management. *Am J Sports Med* 2010;38(3):464-471
- 84 Lovell MR, Iverson GL, Collins MW, et al. Measurement of symptoms following sports-related concussion: reliability and normative data for the post-concussion scale. *Appl Neuropsychol* 2006;13(3):166-174
- 85 Broglio SP, Macciocchi SN, Ferrara MS. Sensitivity of the concussion assessment battery. *Neurosurgery* 2007;60(6):1050-1057, discussion 1057-1058
- 86 Alla S, Sullivan SJ, Hale L, McCrory P. Self-report scales/checklists for the measurement of concussion symptoms: a systematic review. *Br J Sports Med* 2009;43(Suppl 1):i3-i12
- 87 McCrea M. Standardized mental status testing on the sideline after sport-related concussion. *J Athl Train* 2001;36(3):274-279
- 88 McCrea M. Standardized mental status assessment of sports concussion. *Clin J Sport Med* 2001;11(3):176-181
- 89 McCrea M, Barr WB, Guskiewicz K, et al. Standard regression-based methods for measuring recovery after sport-related concussion. *J Int Neuropsychol Soc* 2005;11(1):58-69
- 90 Barr WB, McCrea M. Sensitivity and specificity of standardized neurocognitive testing immediately following sports concussion. *J Int Neuropsychol Soc* 2001;7(6):693-702
- 91 Daniel JC, Nassiri JD, Wilckens J, Land BC. The implementation and use of the standardized assessment of concussion at the U.S. Naval Academy. *Mil Med* 2002;167(10):873-876
- 92 Kennedy CH, Porter Evans J, Chee S, Moore JL, Barth JT, Stuessi KA. Return to combat duty after concussive blast injury. *Arch Clin Neuropsychol* 2012;27(8):817-827
- 93 Guskiewicz KM. Postural stability assessment following concussion: one piece of the puzzle. *Clin J Sport Med* 2001;11(3):182-189
- 94 Giza CC, Kutcher JS, Ashwal S, et al. Summary of evidence-based guideline update: evaluation and management of concussion in sports: report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology* 2013;80(24):2250-2257
- 95 Peterson CL, Ferrara MS, Mrazik M, Piland S, Elliott R. Evaluation of neuropsychological domain scores and postural stability following cerebral concussion in sports. *Clin J Sport Med* 2003;13(4):230-237
- 96 Guskiewicz KM, Ross SE, Marshall SW. Postural stability and neuropsychological deficits after concussion in collegiate athletes. *J Athl Train* 2001;36(3):263-273
- 97 Riemann BL, Guskiewicz KM. Effects of mild head injury on postural stability as measured through clinical balance testing. *J Athl Train* 2000;35(1):19-25
- 98 Finnoff JT, Peterson VJ, Hollman JH, Smith J. Intrarater and interrater reliability of the Balance Error Scoring System (BESS). *PM R* 2009;1(1):50-54
- 99 Maki BE, McLroy WE. Influence of arousal and attention on the control of postural sway. *J Vestib Res* 1996;6(1):53-59
- 100 Horslen BC, Carpenter MG. Arousal, valence and their relative effects on postural control. *Exp Brain Res* 2011;215(1):27-34
- 101 Wada M, Sunaga N, Nagai M. Anxiety affects the postural sway of the antero-posterior axis in college students. *Neurosci Lett* 2001;302(2-3):157-159
- 102 Docherty CL, Valovich McLeod TC, Shultz SJ. Postural control deficits in participants with functional ankle instability as measured by the balance error scoring system. *Clin J Sport Med* 2006;16(3):203-208
- 103 Valovich McLeod TC, Perrin DH, Guskiewicz KM, Shultz SJ, Diamond R, Gansneder BM. Serial administration of clinical concussion assessments and learning effects in healthy young athletes. *Clin J Sport Med* 2004;14(5):287-295
- 104 Eckner JT, Kutcher JS, Broglio SP, Richardson JK. Effect of sport-related concussion on clinically measured simple reaction time. *Br J Sports Med* 2014;48(2):112-118
- 105 Eckner JT, Kutcher JS, Richardson JK. Pilot evaluation of a novel clinical test of reaction time in National Collegiate Athletic Association Division I football players. *J Athl Train* 2010;45(4):327-332
- 106 Eckner JT, Richardson JK, Kim H, Lipps DB, Ashton-Miller JA. A novel clinical test of recognition reaction time in healthy adults. *Psychol Assess* 2012;24(1):249-254
- 107 Eckner JT, Kutcher JS, Richardson JK. Between-seasons test-retest reliability of clinically measured reaction time in National Collegiate Athletic Association Division I athletes. *J Athl Train* 2011;46(4):409-414
- 108 Del Rossi G, Malaguti A, Del Rossi S. Practice effects associated with repeated assessment of a clinical test of reaction time. *J Athl Train* 2014;49(3):356-359
- 109 Barnes GR, Collins CJ. Internally generated smooth eye movement: its dynamic characteristics and role in randomised and predictable pursuit. *Prog Brain Res* 2008;171:441-449
- 110 Lisberger SG, Morris EJ, Tychsen L. Visual motion processing and sensory-motor integration for smooth pursuit eye movements. *Annu Rev Neurosci* 1987;10:97-129
- 111 Galetta MS, Galetta KM, McCrossin J, et al. Saccades and memory: baseline associations of the King-Devick and SCAT2 SAC tests in professional ice hockey players. *J Neurol Sci* 2013;328(1-2):28-31
- 112 Galetta KM, Barrett J, Allen M, et al. The King-Devick test as a determinant of head trauma and concussion in boxers and MMA fighters. *Neurology* 2011;76(17):1456-1462
- 113 Galetta KM, Brandes LE, Maki K, et al. The King-Devick test and sports-related concussion: study of a rapid visual screening tool in a collegiate cohort. *J Neurol Sci* 2011;309(1-2):34-39
- 114 King D, Clark T, Gissane C. Use of a rapid visual screening tool for the assessment of concussion in amateur rugby league: a pilot study. *J Neurol Sci* 2012;320(1-2):16-21
- 115 Echemendia RJ, Bruce JM, Bailey CM, Sanders JF, Arnett P, Vargas G. The utility of post-concussion neuropsychological data in identifying cognitive change following sports-related MTBI in the absence of baseline data. *Clin Neuropsychol* 2012;26(7):1077-1091
- 116 Williamson IJ, Goodman D. Converging evidence for the under-reporting of concussions in youth ice hockey. *Br J Sports Med* 2006;40(2):128-132, discussion 128-132
- 117 Johnson EW, Kegel NE, Collins MW. Neuropsychological assessment of sport-related concussion. *Clin Sports Med* 2011;30(1):73-88, viii-ixviii-ix
- 118 Ellemberg D, Henry LC, Macciocchi SN, Guskiewicz KM, Broglio SP. Advances in sport concussion assessment: from behavioral to brain imaging measures. *J Neurotrauma* 2009;26(12):2365-2382
- 119 Randolph C, McCrea M, Barr WB. Is neuropsychological testing useful in the management of sport-related concussion? *J Athl Train* 2005;40(3):139-152
- 120 Cernich A, Reeves D, Sun W, Bleiberg J. Automated Neuropsychological Assessment Metrics sports medicine battery. *Arch Clin Neuropsychol* 2007;22(Suppl 1):S101-S114
- 121 Iverson GL, Schatz P. Advanced topics in neuropsychological assessment following sport-related concussion. *Brain Inj* 2014;1-13Epub ahead of print
- 122 Schatz P, Pardini JE, Lovell MR, Collins MW, Podell K. Sensitivity and specificity of the ImPACT Test Battery for concussion in athletes. *Arch Clin Neuropsychol* 2006;21(1):91-99
- 123 Broglio SP, Ferrara MS, Macciocchi SN, Baumgartner TA, Elliott R. Test-retest reliability of computerized concussion assessment programs. *J Athl Train* 2007;42(4):509-514
- 124 Schatz P, Sandel N. Sensitivity and specificity of the online version of ImPACT in high school and collegiate athletes. *Am J Sports Med* 2013;41(2):321-326
- 125 Nakayama Y, Covassin T, Schatz P, Nogle S, Kovan J. Examination of the Test-Retest Reliability of a Computerized Neurocognitive Test Battery. *Am J Sports Med* 2014;42(8):2000-2005

- 126 Resch JE, McCrea MA, Cullum CM. Computerized neurocognitive testing in the management of sport-related concussion: an update. *Neuropsychol Rev* 2013;23(4):335–349
- 127 Cole WR, Arrieux JP, Schwab K, Ivins BJ, Qashu FM, Lewis SC. Test-retest reliability of four computerized neurocognitive assessment tools in an active duty military population. *Arch Clin Neuropsychol* 2013;28(7):732–742
- 128 Henry LC, Sandel N. Adolescent Subtest Norms for the IMPACT Neurocognitive Battery. *Appl Neuropsychol Child* 2014;20:1–11. [Epub ahead of print]
- 129 Lovell MR, Solomon GS. Psychometric data for the NFL neuropsychological test battery. *Appl Neuropsychol* 2011;18(3):197–209
- 130 Schmidt JD, Register-Mihalik JK, Mihalik JP, Kerr ZY, Guskiewicz KM. Identifying impairments after concussion: normative data versus individualized baselines. *Med Sci Sports Exerc* 2012;44(9):1621–1628
- 131 Levinson DM, Reeves DL. Monitoring recovery from traumatic brain injury using automated neuropsychological assessment metrics (ANAM V1.0). *Arch Clin Neuropsychol* 1997;12(2):155–166
- 132 Louey AG, Cromer JA, Schembri AJ, et al. Detecting cognitive impairment after concussion: sensitivity of change from baseline and normative data methods using the CogSport/Axon Cognitive Test Battery. *Arch Clin Neuropsychol* 2014;29(5):432–441
- 133 Reeves DL, Bleiberg J, Roebuck-Spencer T, et al. Reference values for performance on the Automated Neuropsychological Assessment Metrics V3.0 in an active duty military sample. *Mil Med* 2006;171(10):982–994
- 134 Vincent AS, Roebuck-Spencer T, Gilliland K, Schlegel R. Automated Neuropsychological Assessment Metrics (v4) Traumatic Brain Injury Battery: military normative data. *Mil Med* 2012;177(3):256–269
- 135 Roebuck-Spencer TM, Vincent AS, Schlegel RE, Gilliland K. Evidence for added value of baseline testing in computer-based cognitive assessment. *J Athl Train* 2013;48(4):499–505
- 136 Kuhn AW, Solomon GS. Supervision and computerized neurocognitive baseline test performance in high school athletes: an initial investigation. *J Athl Train* 2014;49(6):800–805
- 137 Patel AV, Mihalik JP, Notebaert AJ, Guskiewicz KM, Prentice WE. Neuropsychological performance, postural stability, and symptoms after dehydration. *J Athl Train* 2007;42(1):66–75
- 138 Bailey CM, Samples HL, Broshek DK, Freeman JR, Barth JT. The relationship between psychological distress and baseline sports-related concussion testing. *Clin J Sport Med* 2010;20(4):272–277
- 139 Lewis MS, Snyder PJ, Pietrzak RH, Darby D, Feldman RA, Maruff P. The effect of acute increase in urge to void on cognitive function in healthy adults. *NeuroUrol Urodyn* 2011;30(1):183–187
- 140 Hutchison M, Comper P, Mainwaring L, Richards D. The influence of musculoskeletal injury on cognition: implications for concussion research. *Am J Sports Med* 2011;39(11):2331–2337
- 141 Kane RL, Kay GG. Computerized assessment in neuropsychology: a review of tests and test batteries. *Neuropsychol Rev* 1992;3(1):1–117
- 142 Collie A, Maruff P, Makdissi M, McCrory P, McStephen M, Darby D. CogSport: reliability and correlation with conventional cognitive tests used in postconcussion medical evaluations. *Clin J Sport Med* 2003;13(1):28–32
- 143 Collie A, Maruff P, Makdissi M, McStephen M, Darby DG, McCrory P. Statistical procedures for determining the extent of cognitive change following concussion. *Br J Sports Med* 2004;38(3):273–278
- 144 Falsetti MG, Maruff P, Collie A, Darby DG, McStephen M. Qualitative similarities in cognitive impairment associated with 24 h of sustained wakefulness and a blood alcohol concentration of 0.05%. *J Sleep Res* 2003;12(4):265–274
- 145 Collie A, Maruff P, Darby DG, McStephen M. The effects of practice on the cognitive test performance of neurologically normal individuals assessed at brief test-retest intervals. *J Int Neuropsychol Soc* 2003;9(3):419–428
- 146 Collie A, Darby DG, Falsetti MG, Silbert BS, Maruff P. Determining the extent of cognitive change after coronary surgery: a review of statistical procedures. *Ann Thorac Surg* 2002;73(6):2005–2011
- 147 Jagoda AS, Bazarian JJ, Bruns JJ Jr, et al; American College of Emergency Physicians; Centers for Disease Control and Prevention. Clinical policy: neuroimaging and decisionmaking in adult mild traumatic brain injury in the acute setting. *Ann Emerg Med* 2008;52(6):714–748
- 148 Kuppermann N, Holmes JF, Dayan PS, et al; Pediatric Emergency Care Applied Research Network (PECARN). Identification of children at very low risk of clinically-important brain injuries after head trauma: a prospective cohort study. *Lancet* 2009;374(9696):1160–1170
- 149 Nigrovic LE, Lee LK, Hoyle J, et al; Traumatic Brain Injury (TBI) Working Group of Pediatric Emergency Care Applied Research Network (PECARN). Prevalence of clinically important traumatic brain injuries in children with minor blunt head trauma and isolated severe injury mechanisms. *Arch Pediatr Adolesc Med* 2012;166(4):356–361
- 150 Schonfeld D, Bressan S, Da Dalt L, Henien MN, Winnett JA, Nigrovic LE. Pediatric Emergency Care Applied Research Network head injury clinical prediction rules are reliable in practice. *Arch Dis Child* 2014;99(5):427–431
- 151 Nigrovic LE, Schunk JE, Foerster A, et al; Traumatic Brain Injury Group for the Pediatric Emergency Care Applied Research Network. The effect of observation on cranial computed tomography utilization for children after blunt head trauma. *Pediatrics* 2011;127(6):1067–1073
- 152 Brenner DJ. Estimating cancer risks from pediatric CT: going from the qualitative to the quantitative. *Pediatr Radiol* 2002;32(4):228–1, discussion 242–244
- 153 Brenner DJ. What we know and what we don't know about cancer risks associated with radiation doses from radiological imaging. *Br J Radiol* 2014;87(1035):20130629
- 154 Kashluba S, Hanks RA, Casey JE, Millis SR. Neuropsychologic and functional outcome after complicated mild traumatic brain injury. *Arch Phys Med Rehabil* 2008;89(5):904–911
- 155 Sadowski-Cron C, Schneider J, Senn P, Radanov BP, Ballinari P, Zimmermann H. Patients with mild traumatic brain injury: immediate and long-term outcome compared to intra-cranial injuries on CT scan. *Brain Inj* 2006;20(11):1131–1137
- 156 Yuh EL, Cooper SR, Ferguson AR, Manley GT. Quantitative CT improves outcome prediction in acute traumatic brain injury. *J Neurotrauma* 2012;29(5):735–746
- 157 Yuh EL, Cooper SR, Mukherjee P, et al. Diffusion tensor imaging for outcome prediction in mild traumatic brain injury: a TRACK-TBI study. *J Neurotrauma* 2014;31(17):1457–1477
- 158 Yuh EL, Mukherjee P, Lingsma HF, et al; TRACK-TBI Investigators. Magnetic resonance imaging improves 3-month outcome prediction in mild traumatic brain injury. *Ann Neurol* 2013;73(2):224–235
- 159 Guskiewicz KM, Weaver NL, Padua DA, Garrett WE Jr. Epidemiology of concussion in collegiate and high school football players. *Am J Sports Med* 2000;28(5):643–650
- 160 McCrea M, Guskiewicz K, Randolph C, et al. Effects of a symptom-free waiting period on clinical outcome and risk of reinjury after sport-related concussion. *Neurosurgery* 2009;65(5):876–882, discussion 882–883
- 161 Eisenberg MA, Andrea J, Meehan W, Mannix R. Time interval between concussions and symptom duration. *Pediatrics* 2013;132(1):8–17
- 162 National Collegiate Athletic Association. Sports-related concussion. In: Klossner D, ed. 2013–14 NCAA Sports Medicine Handbook. 24th ed. Indianapolis, IN: National Collegiate Athletic Association; 2013:56–66

- 163 National Collegiate Athletic Association. Irick E, ed. NCAA Sports Sponsorship and Participation Rates Report, 1981–82–2012–13. Indianapolis, IN: NCAA; 2013
- 164 Baugh CM, Kroshus E, Daneshvar DH, Filali NA, Hiscox MJ, Glantz LH. Concussion management in United States college sports: compliance with National Collegiate Athletic Association Concussion Policy and areas for improvement. *Am J Sports Med* 2014; Epub ahead of print
- 165 Harmon KG, Drezner JA, Gammons M, et al. American Medical Society for Sports Medicine position statement: concussion in sport. *Br J Sports Med* 2013;47(1):15–26
- 166 Thomas E. Life after concussion: a balancing act. *Pediatr Nurs* 2013;39(6):265–299, 299
- 167 Gibson S, Nigrovic LE, O'Brien M, Meehan WP III. The effect of recommending cognitive rest on recovery from sport-related concussion. *Brain Inj* 2013;27(7-8):839–842
- 168 Moser RS, Glatts C, Schatz P. Efficacy of immediate and delayed cognitive and physical rest for treatment of sports-related concussion. *J Pediatr* 2012;161(5):922–926
- 169 Schneider KJ, Iverson GL, Emery CA, McCrory P, Herring SA, Meeuwisse WH. The effects of rest and treatment following sport-related concussion: a systematic review of the literature. *Br J Sports Med* 2013;47(5):304–307
- 170 Ponsford J, Willmott C, Rothwell A, et al. Impact of early intervention on outcome after mild traumatic brain injury in children. *Pediatrics* 2001;108(6):1297–1303
- 171 Mittenberg W, Tremont G, Zielinski RE, Fichera S, Rayls KR. Cognitive-behavioral prevention of postconcussion syndrome. *Arch Clin Neuropsychol* 1996;11(2):139–145
- 172 Cortesi F, Giannotti F, Sebastiani T, Panunzi S, Valente D. Controlled-release melatonin, singly and combined with cognitive behavioural therapy, for persistent insomnia in children with autism spectrum disorders: a randomized placebo-controlled trial. *J Sleep Res* 2012;21(6):700–709
- 173 Covassin T, Elbin RJ, Harris W, Parker T, Kontos A. The role of age and sex in symptoms, neurocognitive performance, and postural stability in athletes after concussion. *Am J Sports Med* 2012; 40(6):1303–1312
- 174 Covassin T, Elbin RJ III, Larson E, Kontos AP. Sex and age differences in depression and baseline sport-related concussion neurocognitive performance and symptoms. *Clin J Sport Med* 2012; 22(2):98–104
- 175 Collins MW, Kontos AP, Reynolds E, Murawski CD, Fu FH. A comprehensive, targeted approach to the clinical care of athletes following sport-related concussion. *Knee Surg Sports Traumatol Arthrosc* 2014;22(2):235–246
- 176 Larun L, Nordheim LV, Ekeland E, Hagen KB, Heian F. Exercise in prevention and treatment of anxiety and depression among children and young people. *Cochrane Database Syst Rev* 2006; 3(3):CD004691
- 177 Rimer J, Dwan K, Lawlor DA, et al. Exercise for depression. *Cochrane Database Syst Rev* 2012;7:CD004366
- 178 Leddy JJ, Kozlowski K, Donnelly JP, Pendergast DR, Epstein LH, Willer B. A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome. *Clin J Sport Med* 2010;20(1):21–27
- 179 Leddy JJ, Cox JL, Baker JG, et al. Exercise treatment for postconcussion syndrome: a pilot study of changes in functional magnetic resonance imaging activation, physiology, and symptoms. *J Head Trauma Rehabil* 2013;28(4):241–249
- 180 Ownsworth TL, Oei TP. Depression after traumatic brain injury: conceptualization and treatment considerations. *Brain Inj* 1998; 12(9):735–751
- 181 Kang HK, Natelson BH, Mahan CM, Lee KY, Murphy FM. Post-traumatic stress disorder and chronic fatigue syndrome-like illness among Gulf War veterans: a population-based survey of 30,000 veterans. *Am J Epidemiol* 2003;157(2):141–148
- 182 Boyle E, Cancelliere C, Hartvigsen J, Carroll LJ, Holm LW, Cassidy JD. Systematic review of prognosis after mild traumatic brain injury in the military: results of the International Collaboration on Mild Traumatic Brain Injury Prognosis. *Arch Phys Med Rehabil* 2014;95(3, Suppl):S230–S237
- 183 Kennedy JE, Leal FO, Lewis JD, Cullen MA, Amador RR. Posttraumatic stress symptoms in OIF/OEF service members with blast-related and non-blast-related mild TBI. *NeuroRehabilitation* 2010;26(3):223–231
- 184 Hoge CW, McGurk D, Thomas JL, Cox AL, Engel CC, Castro CA. Mild traumatic brain injury in U.S. Soldiers returning from Iraq. *N Engl J Med* 2008;358(5):453–463
- 185 Sher L. Suicide in war veterans: the role of comorbidity of PTSD and depression. *Expert Rev Neurother* 2009;9(7): 921–923
- 186 Simpson TL, Kaysen D, Bowen S, et al. PTSD symptoms, substance use, and vipassana meditation among incarcerated individuals. *J Trauma Stress* 2007;20(3):239–249
- 187 Bryan CJ, Clemans TA. Repetitive traumatic brain injury, psychological symptoms, and suicide risk in a clinical sample of deployed military personnel. *JAMA Psychiatry* 2013;70(7):686–691