Traumatic Brain Injury

A Clinician's Guide to Diagnosis, Management, and Rehabilitation

Jack W. Tsao
Editor

Second Edition

Springer

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For Veronica, Emmanuel, Joan, Grace, Peter, Anna, and Mike

Preface

The first edition of *Traumatic Brain Injury: A Clinician's Guide to Diagnosis, Management, and Rehabilitation*, published in 2012, was written to enable medical professionals to quickly learn about the latest issues and treatments in this evolving clinical field. Since that time, there has been increased public awareness of the clinical consequences of even the mildest of head injuries, and the numerous advances in the areas of diagnosis, evaluation, treatment, and pathophysiology have resulted from a concerted effort of countries around the world to increase research funding.

This second edition continues to focus on mild traumatic brain injury—or concussion—and contains updates to all the original chapters as well as adds new chapters addressing clinical sequelae, including pediatric concussion, visual changes, chronic traumatic encephalopathy, and blast-related TBI, the latter two being areas of intense research efforts currently. The chapter authors were asked to focus on key issues of which practicing clinicians should be aware in order to provide the best care to their patients. An updated appendix of ICD codes is included.

I would like to thank my family for their support in the writing and editing process; my colleagues who generously contributed their time to updating or writing new chapters; Richard Lansing, the publishing editor who encouraged me to edit this second edition; and Elizabeth Corra, the development editor who helped guide this edition to its completion. Finally, as many of the authors of this edition continue to serve as US military officers or government employees, I am including the disclaimer here: The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Departments of the Navy or Army, the Department of Defense, or the Department of Veterans Affairs.

Memphis, TN, USA — Jack W. Tsao

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Overview of Traumatic Brain Injury (TBI)

David F. Moore, Michael Jaffee, Geoffrey Ling, and Raul Radovitzky

Historical Perspective

Accounts of neurological trauma are present in the *Iliad* and *Odyssey* of Homer from Greek antiquity where concepts consistent with interpretation loss of consciousness, penetrating brain injury, spinal cord injury, brachial plexus, and nerve injury are present. These injury concepts of the nervous system are well summarized with direct translation from ancient Greek in two review articles by Walshe [1] and Sablas [2]. One important aspect of these oral tradition epics to the ancient Greeks may have been to preserve warrior knowledge about injury vulnerability, allowing more formalized military training. It is clear that even in antiquity, traumatic brain injury (TBI) was described both in the military and civilian context.

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The historical account of concussion is well summarized and described by the paper by McCrory and Berkovic [3]. Initial use of the term "concussion," in the modern sense of an alteration or temporary loss of adaptive brain function or an abnormal brain physiological state, as opposed to distinct brain injury, was used by the medieval Persian physician Rhazes (Muhammad ibn Zakariyā Rāzī**,** 826–925 AD). Subsequent to this and with Chauliac (1300–1368 AD), the concept of a brain concussion or "commotio cerebri" with a relatively benign outcome from "contusio cerebri" or brain injury, such as a skull fracture with a poor outcome, became accepted in Western medicine with some variation. In more recent discussion the consideration of a structural versus a functional cause of concussion has been considered in light of modern medical advances and technologies but still contains significant indeterminacies depending on the length scale of the approach. For example, in acute concussion neuroimaging is typically negative, yet with more extended techniques, such as diffusion tensor imaging and susceptibility weighted imaging, previously unrecognized lesions are becoming increasingly appreciated indicating sustainment of structural abnormalities. The conception of the length scale of injury is fundamental to the subsequent discussion of TBI, since, at a molecular level, membrane disruption may result in alteration in membrane chan-

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nel physiology or mechanoporation with resultant abnormal ionic fluxes and altered cellular and axonal function. Distinct examples of pathological sensitivity to brain trauma are present in abnormalities of calcium channel subunit *CACNA1A* and CACH (Childhood Ataxia and CNS Hypomyelination) [4, 5].

Complexity of Intracranial Anatomy

The brain is a uniquely anisotropic organ with the gyrencephalic cortical gray matter, broadly orthogonal white matter fascicles, and subcortical gray matter nuclei together with multiple solid fluid interfaces between the brain parenchyma and the cerebrospinal fluid (CSF) both internally as represented by the ventricles and externally by the subarachnoid space. The entire brain is tethered by the dura together with the bridging veins and other vascular structures surrounded by the CSF fluid cushion of the subarachnoid space. The skull represents a further protective layer of similar complexity with the diploic bone structure and numerous air sinus cavities together with foramina for exiting and entrance of various neurovascular bundles. The complexity of the intracranial contents is well illustrated in Fig. 1, an axial section of the brain from the Visible Human Project [6].

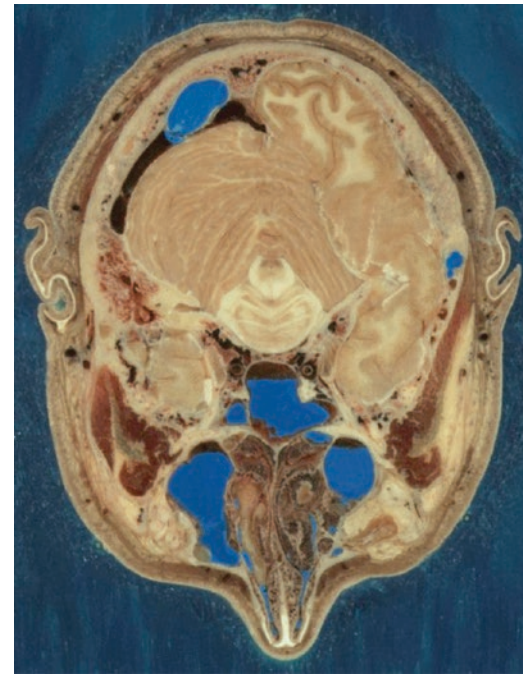

Fig. 1 Illustrating the intracranial contents illustrating the diploic nature of the skull bone and the numerous air sinus spaces together with the venous sinuses and dural sheathing. The gyrencephalic quality of the cortical ribbon is well seen in the occipital–temporal region. The complexity of brain anatomy has significant implications for the transmission of mechanical forces that may injure brain tissue. In particular this is seen in the military context across impact to penetrating to blast brain injury. (Source: Visible Human Project. http://www.nlm.nih.gov/research/visible/visible_human.html. Public Domain)

Definition of Traumatic Head Injury

The current definition of TBI is phenomenological. Often there is confusion in the nosology of TBI especially in relation to mild TBI (mTBI), a term that implicitly refers to the TBI event consistent with acute concussion. TBI is categorized according to the clinical pillars of post-traumatic amnesia (PTA) and/or a disturbance of consciousness – either alteration of consciousness (AOC) or loss of consciousness (LOC). These clinical features, although correlated, allow for independent diagnosis of TBI severity. The overall TBI diagnosis is due to the severity of *Primary Traumatic Brain Damage* – that is, brain injury that results from mechanical forces producing tissue deformation at the moment of injury with direct damage to blood vessels, axons, neurons, and glia. The Glasgow Coma Scale (GCS) is also used as a TBI severity and diagnostic scale with mTBI having a GCS range of 13–15, moderate TBI a GCS range of 9–12, and severe TBI a GCS of 3–8. *Secondary Traumatic Brain Damage* on the other hand, is

Table 1 Ascertainment of TBI according to the accepted severity scales. Definitions of TBI spectrum

GCS	LOC	PTA	TBI
13–15	<1 h	<24 h	Mild or mTBI
9–12	>1 h and < 24 h	>24 h and < 7 days	Moderate
3–8	>24 h	>7 days	Severe

by definition, due to the complications of primary damage, including brain tissue hypoxia, ischemia, hydrocephalus, raised intracranial pressure (ICP), and central nervous system (CNS) infection. The TBI spectrum definitions are summarized in Table 1. TBI is dichotomized into penetrating (pTBI) and closed TBI (cTBI), with the sub-classification of cTBI into mild, moderate, and severe TBI. Although there is variation between epidemiological studies and it is a truism that all epidemiological studies are in some degree biased due to a trade-off between the veracity of ascertainment and the extent of the population sampled, rough categorization suggests ~ 17% of cTBI being severe with ~ 13% being moderate and ~ 70% being mTBI.

The above classification of TBI is inherently clinical and dependent on either direct observation or self-report. The current clinical trend is to attempt to redefine categorization of TBI in a patho-anatomic framework [7]. This is motivated, in part, by the recurrent failure of randomized clinical trials (RCTs) in TBI, including the initial promising results of progesterone in moderate TBI but also by a drive for standardization with the development of common data elements (CDE) to facilitate ongoing and new RCTs [8–11]. CDEs will also be particularly important in cross-sectional and longitudinal epidemiology studies, allowing for "core" datasets to be acquired in studies with undoubted comparative value between study populations. A key epidemiological fact concerning TBI is that ~ 1.7 million civilian TBIs occur annually in the United States with a cost estimated at 60 billion dollars both in direct medical costs and in indirect costs due to lost productivity to society [12, 13].

TBI Spectrum: Neuropathology and Acute, Subacute, and Chronic Effects

In primary TBI the spectrum of injury may range from diffuse or multifocal, resulting in diffuse axonal injury (DAI) and diffuse vascular injury (DVI), to focal, with intracerebral hemorrhage, subdural hemorrhage, epidural hemorrhage, and subarachnoid hemorrhage [14]. Other injuries include direct axonal injury, direct brain laceration, and contusion. Injuries from secondary TBI may also be diffuse, such as diffuse hypoxic-ischemic damage, and diffuse brain swelling, or focal, with focal hypoxic ischemic injury and focal brain swelling. Acute moderate and severe TBI may often require neurosurgical intervention, while mTBI or concussion typically requires limited observation and intervention, with recuperation occurring over several days to weeks. The prolonged sequelae of TBIs are an opportunity for extensive rehabilitation care and therapeutic intervention. Of particular interest is the potential for metabolic abnormalities after concussion that, if not adequately resolved, may predispose the brain to more extensive damage if a further concussion occurs during the period of vulnerability, the second impact syndrome [15, 16] (Fig. 2a–h).

Concussion Biology and Mechanism

The neurobiology of concussion is incompletely understood, and this has resulted in several theories, ranging from interference to the reticular activating system to interference with the cholinergic reticular inhibitory system to a paroxysmal depolarization shift resulting in "kindling" and a potential convulsive episode resulting in concussion (Walker's Convulsive Theory) [15, 17]. From clinical neurology it is a clinical maxim that an alteration in consciousness results from either a bi-hemispheric process or a process in the posterior fossa. In relation to AOC and LOC, it is probable that most concussive processes result from a bilateral process suggesting more of a convulsive process secondary to a paroxysmal depolarization shift, although this cannot be stated with certainty. Similar reasoning is applicable to PTA with a resulting failure to lay down memory engrams bilaterally – the memory consolidation hypothesis.

The mechanical events precipitating concussion have been the subject of debate since the 1940s. In a short abstract by Derek Denny-Brown

and Russell Ritchie from 1940 [18], nembutal-anaesthetized cats were subjected to a concussive blow with the requirement that the head was able to undergo acceleration with associated translation and rotational effects. The blow was able to induce death without any rise in ICP and failed to result in concussion if the head was restrained and did not undergo acceleration. The cause of death appeared to be respiratory depression, but all brainstem reflexes were depressed, with the brainstem respiratory centers being the most sensitive. Denny-Brown commented that "momentary deformity of the skull and stimulation of superficial structures, therefore, appear to play no part" and finishes with "the nervous effect of a blow is, thus, considered to be due to the physical acceleration directly transmitted to each and every centre" [18]. A threshold of 23'/sec was found for the cat with a higher value for the Macaque monkey. Subsequent to this, Holbourn, in 1943, suggested that, due to the incompressible nature of the brain, linear acceleration would be unable to result in brain tissue injury; however, angular acceleration would result in shear strain and subsequent brain injury [19]. This was countered by Gurdjian and Lissner in 1944 [20] who suggested that concussion resulted from the pressure differential and the induced shearing strain on the brainstem with little reference to rotational injury.

More advanced interpretations of TBI using Newton-Euler equations describing combined translational and rotational dynamics indicate that movement may occur in all six degrees of freedom where the coordinate frame does not correspond to center of mass of the rigid body. The equations clearly indicate that the translational and angular accelerations are coupled, resulting in both force and torque components on the brain. The exact components of torque

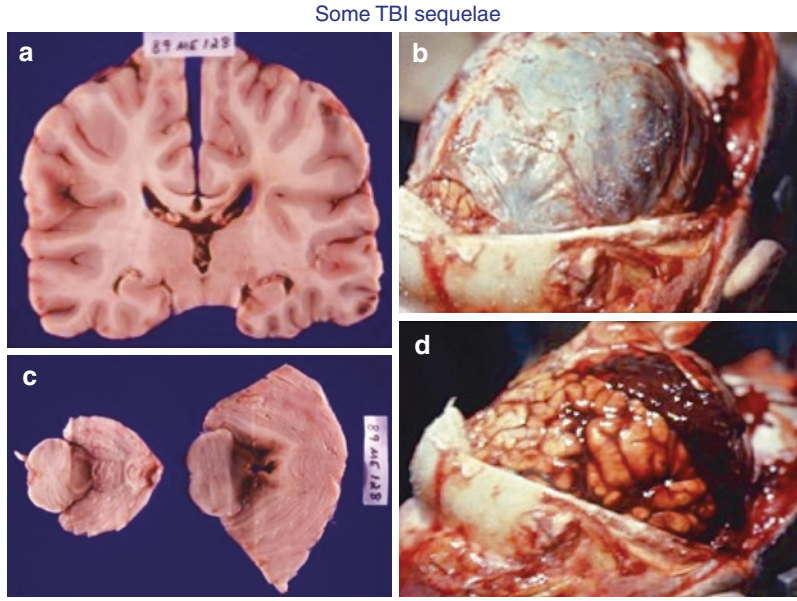

Fig. 2 Illustration of the neuropathology of TBI. (**a**, **c**): illustrate the gross neuropathology of diffuse axonal injury with white matter hemorrhage in the corpus callosum (**a**) and in the pontine white matter (**c**). (**b**, **d**): illustrate a subdural hematoma with (**b**) showing the dura intact and (**d**) the underlying hematoma with the dura reflected. (**e**): demonstrates cerebral contusion with bifrontal and bitemporal contusions. (**f**): left side of image shows a coronal section with edematous and swollen brain compared to normal brain tissue on the right side. (**g**): swollen optic nerve head in sagittal section due to chronically raised ICP. (**h**): delayed apoptosis of neuronal cells following TBI

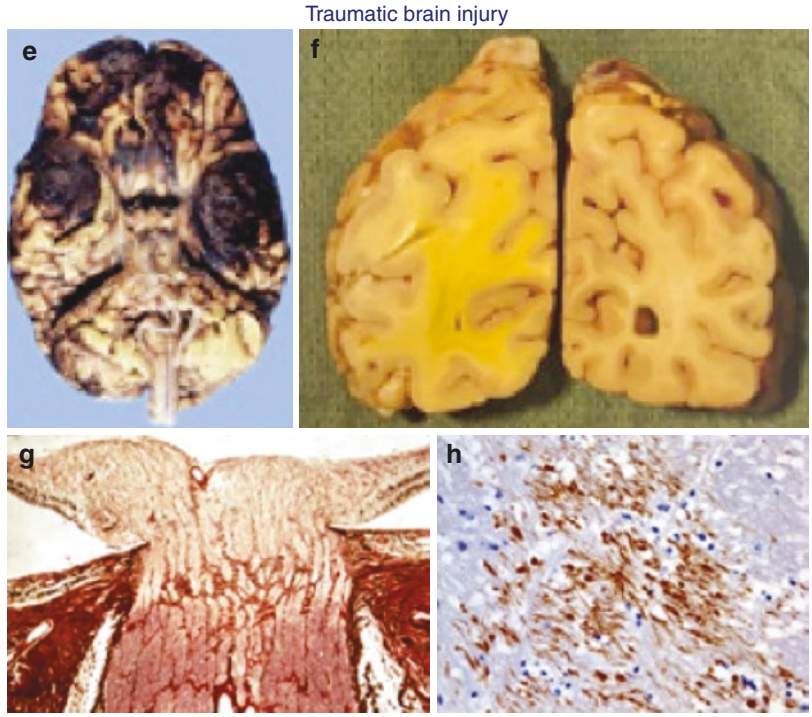

Fig. 2 (continued)

and force will depend on the site and directionality of skull impact together with the duration of the mechanical jolt [21]. The mobility of the skull on the neck also probably contributes considerably to the variation in the forces and, thereby, acceleration components experienced by the brain.

Constitutive Properties

The constitutive property of a material or tissue is the equation and parameter relationship specific for the tissue between the applied stress field (σ) and strain deformation (ε). Typically, this may have a higher-order tensor representation and involve varying elements of elasticity and viscosity. The unique nature of the brain compared to more typical engineering material is that it is a soft material, and further, it is biphasic in that it consists of a water-like component with an embedded matrix resulting in a poro-elastic tissue. Poro-elastic materials have different properties from more conventional materials especially in terms of wave propagation, where poro-elastic mediums support both dilational and transverse waves but also includes a further dilational wave that is of lower propagation velocity and termed by Biot as a dilational wave of the second kind [22, 23]. This consideration and analysis was derived from propagation of elastic waves, with the direction of propagation of the wave being longitudinal as opposed to rotational, or transverse, where the direction of wave motion is normal to the direction of propagation, resulting in a shear wave within the tissue. It is not at all obvious how a pore-elastic medium interacts with blast or shock wave propagation through a tissue. In Fig. 3 a lumped isotropic model of brain tissue is presented with varying mechanical elements that account for tissue visco-elasticity, shear thickening, pore elasticity, and nonlinear tissue relaxation to stress. The brain is highly anisotro-

pic with the potential for material properties to alter in a directional and regional manner so that the constitutive property of white matter is likely to differ from gray matter. The correct characterization of the material and constitutive properties of tissue is an essential prerequisite to the accurate validation of complex finite element models used to enhance understanding of mechanical and blast-related TBI.

Woodpecker Analogy

The woodpecker is a particular instructive "experiment of nature" in relation to concussion. It is a possibility that further understanding of the biological and physical characterization of the woodpecker in relation to head impact may define those biological features that are adaptive and protective against concussion (Fig. 4). In a paper by Oda and colleagues [24], the authors use finite element models (FEM) of the woodpecker skull and examined the properties of the woodpecker that resulted in concussive stress wave dissipation. The analysis found that the unique shape of the head and neck tended to channel the stress wave away from the skull into the neck while the brain is tightly tethered by the dura and the small cerebrospinal fluid space (CSF). Further an adaptive hyoid bone anatomy together with the cancellous nature of the skull bone results in further stress dissipation from the concussion wave due to woodpecker head impact [24].

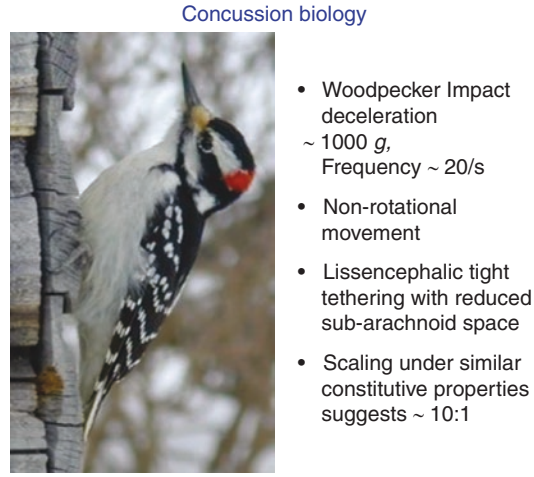

Fig. 4 Concussion biology. The woodpecker species is uniquely adapted to high impact loading on the beak and head with unique biological adaptations to prevent concussion

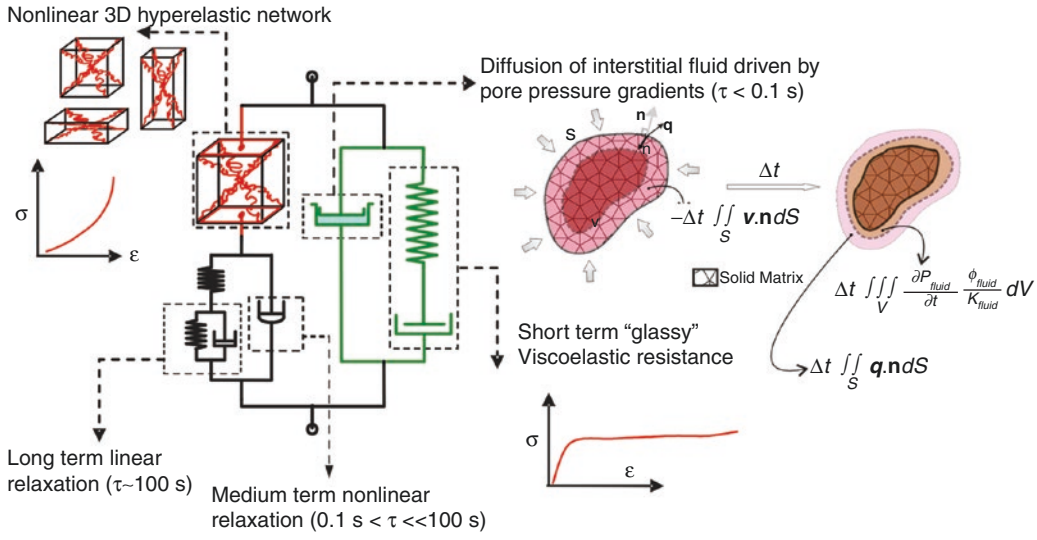

Fig. 3 Constitutive model of brain tissue illustrating visco-elasticity, shear thickening to increasing strain rate, tissue pore elasticity, and nonlinear relaxation effects to mechanical stress. (Courtesy of Dr. Simona Socrate, MIT, and The Institute of Soldier Nanotechnology)

The ability of the woodpecker to sustain repeated concussive impact without biological effect is of significance and bears further study. The potential to inform preventive strategies to minimize concussion should not be underestimated. For example, consideration of head and neck posture during an impending concussion with increased neck rigidity may prevent extensive rotational acceleration and the incipient development of concussion. Recent preliminary data suggest that this biological adaptation may not be so complete. As noted by McKee et al. [25], the accumulation of tau protein appears to be correlated with repeated concussion, resulting in the "end-stage" brain disease now termed chronic traumatic encephalopathy or CTE. Following from this, preliminary data from Farah and colleagues [26] examined a small series of woodpecker brains against control avian species with no such ecological niche and found histological evidence of tau deposition in the woodpecker as opposed to avian controls. Such preliminary data are of substantial interest but needs to be isolated with longitudinal prospective comparisons of a "wild woodpecker" cohort exposed to "natural" concussion compared within species to an atraumatic non-concussed woodpecker cohort in order to establish biological relevance.

Persistent Post-concussive Symptoms

A number of patients after a concussion fail to resolve clinically but develop persistent post-concussive symptoms [27]. This constellation of symptoms usually involves headaches, imbalance or postural disequilibrium and memory difficulties that persist for several months from the concussive event (*International Classification of Diseases, 10th Revision, Criteria for Postconcussion Syndrome (Code 310–2)*. The symptoms are often refractory to treatment but generally abate over months to years [28]. Up to about 15% of patients can be affected in civilian injury and concussion, but these statistics are study and population dependent. Using an Illness Perception Model, Whittaker and colleagues [29] were able to predict persistence of post-concussive symptoms in 80% of diagnosed patients in their population. The work suggests that patients may incorrectly attribute commonly prevalent symptoms to the concussive injury and become more at risk for development of persistent post-concussive symptoms [29]. In a follow-on editorial, Wood comments on the efficacy of cognitive-behavioral therapeutic approaches in persistent post-concussive symptoms using brief early interventions [30]. Such studies may point to efficient mechanisms of preventing this important comorbidity of concussion in the civilian head injury population; however, the possibility of true structural and organic changes must be considered especially due to the known plasticity of the CNS [31].

Strain-Rate Continuum of TBI

Stress is the force per unit area within the tissue, with the resulting strain deformation field depending on the applied stress and the constitutive properties of the tissue. These measurements are often performed in a quasi-static fashion where this may allow reversible mechanical changes in the tissue during application of the stress fields both in compression or tension. For TBI, traumatic events occur in a variety of ways such as during motor vehicle crashes or following penetrating head injury from a bullet wound or blast-associated traumatic head injury. The rate at which stress is applied to the head or brain differs under these differing conditions but is related to the strain rate, with vehicular head injury occurring at a strain rate $< 500\ s^{-1}$, while penetrating injury occurs at a strain rate $\sim 2000\ s^{-1}$. With blast-associated head injury, the rate of strain can be in the range of ~ 2000 to $10{,}000\ s^{-1}$. It is, therefore, possible to consider TBI from these diverse etiologies across a strain-rate continuum with the constitutive tissue properties often responding in a strain-rate-dependent manner [32]. This is particularly important where the requirement

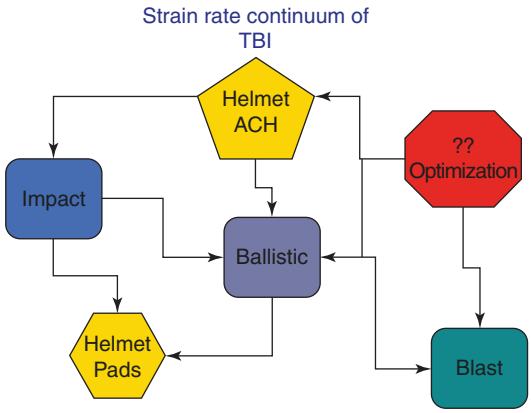

Fig. 5 Strain-rate continuum for traumatic brain injury where the optimization of PPE against impact injury may be enhanced by optimization of helmet pads placed between the helmet shell and the head. The ballistic protection is provided by the material composition of the helmet shell, while mitigation of blast injury may require further head and facial coverage by appropriate protective materials. The simultaneous optimization and characterization of these diverse material properties capable of preventing head injury across the strain-rate domain is formidable

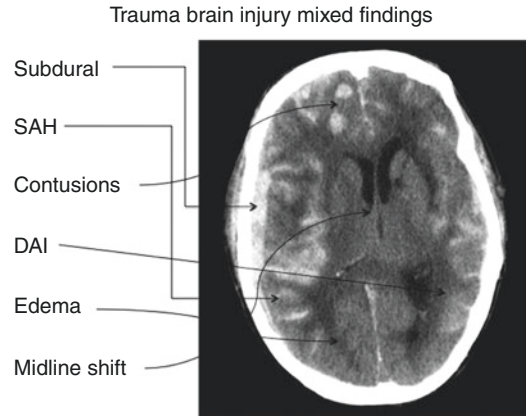

Fig. 6 Computed tomography (CT) axial image illustrating multiple simultaneous pathologies of subdural hematoma, subarachnoid hemorrhage, cerebral contusions, diffuse axonal injury, cerebral edema, and herniation syndromes with midline shift. (CT image courtesy of Dr. James Smirniotopoulos, Radiology, USUHS, and Dr. Gerard Riedy, Radiology, WRAMC)

is to design helmets for prevention of head injury and to obtain full characterization of possible tissue injury parameters. For personal protective equipment (PPE), such as the advanced combat helmet (ACH), it is an exceptionally difficult engineering optimization problem to account for mitigation across all the strain-rate domains. This is illustrated in Fig. 5.

Neuroimaging of TBI

In recent years, the rapid advances of neuroimaging of both structure and function have allowed extensive clinical characterization of TBI both for immediate patient clinical care and for clinical investigation and research purposes. It is now possible to understand various subcategories of TBI, such as DAI with more investigative techniques, including diffusion tensor imaging (DTI) with imaging metrics of fractional anisotropy (FA), mean diffusivity (MD), and radial and axial diffusivity [31, 33–45]. The DTI studies performed, in general, indicated reduction in FA with increases in isotropic DTI metrics such as MD. Injury severity is less in concussion or mTBI, with some resolution appearing to occur across time, although there are currently only a limited number of longitudinal DTI studies in TBI [46]. It can be anticipated that greater use of positron emission tomography and single-photon emission tomography together with functional magnetic resonance imaging will more fully explore the aggregate metabolic, neurochemical, and functional neuronal changes in both resting connectivity and task-related connectivity in TBI. A particularly significant area where noninvasive neuroimaging is likely to contribute to substantial clinical insights is in disorders of consciousness, including in persistent vegetative states and emerging levels of consciousness from the minimal conscious state through to normal conscious cognitive states. The complexity of TBI as highlighted is well illustrated in Fig. 6, where multiple pathological processes are seen that simultaneously play in a single patient.

Military Medicine Perspective on Brain Injury

The effect of blast in relation to TBI has been well described since World War I with shell shock and concussion, particularly in the clini-

cal descriptions of Gordon Holmes (1876–1965) [47]. The contingency operations in Iraq (Operation Iraqi Freedom, OIF) and Afghanistan (Operation Enduring Freedom, OEF) have led to a resurgence of research on the effects of blast and blast-associated polytrauma, probably due to the asymmetrical nature of the conflicts and the extensive use of improvised explosive devices (IEDs). Part of the spectrum of blast-associated polytrauma includes the full range of TBI and, in particular, blast-associated concussion or mTBI. Current estimate for blast-associated TBI is ~ 130,000, with US military service members since 2003 with ~ 4.5% of service members having persistent post-concussional symptoms (http://www.dvbic.org/TBI-Numbers.aspx), Blast may be defined as an "in the atmosphere" explosion characterized by the release of energy in a short period of time and within a small volume resulting in the creation of a nonlinear shock and pressure wave of finite amplitude, spreading from the source of the explosion [48]. The energy conversion from a conventional blast can be chemical, electrical, thermal, and kinetic or pressure energy (Fig. 7). The kinetic energy of the blast is associated with fragments and results in their expulsion in advance of the shock wavefront.

The "ideal case" of a blast pressure wave is the Friedlander waveform with a rapid rise time

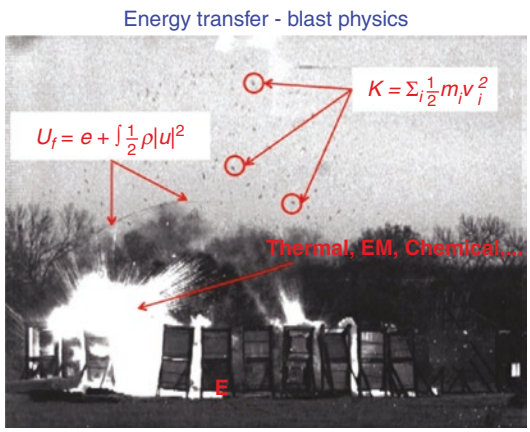

Fig. 7 Energy conversion (E) associated with a blast wave illustrating the shock wavefront together with fragment kinetic energy. Other energy components are the blast-associated electromagnetic (EM) pulse, thermal energy, and chemical conversion

to the peak positive pressure above atmospheric pressure, with the overpressure followed by an exponential pressure fall-off together with a relatively prolonged sub-atmospheric underpressure. Typically, the timescale of the total explosive pressure event is tens of milliseconds. The prolonged underpressure component of the pressure waveform may exceed the critical tensile strength of the fluid component of a tissue, thus allowing the development of cavitation.

Blast injury is defined as *primary* where injury is related to the shock wave overpressure and underpressure propagation through the tissue. *Secondary* blast injury occurs from blast-associated fragments or shrapnel tissue injury. *Tertiary* injury is secondary to falling debris or throwing of the dismounted soldier or vehicle with subsequent tissue injury. *Quaternary* injury develops from a variety of physical processes associated with explosive detonation, such as thermal and/or toxic detonation products, while *quinary* injuries refer to the environmental hazard remaining after an explosive detonation [49–52].

The effects of primary blast on the CNS are still unclear, but in military concussion it is unusual to be exposed solely to primary blast; rather such exposure is associated most commonly with tertiary blast injury [53]. For this reason blast-associated CNS injury is better considered as a constellation of blast component exposures resulting in a blast(+) syndrome of CNS injury. This results in the brain being exposed to mechanical events across the strain-rate continuum as previously discussed. The relationship of particular aspects of the blast wave exposure (that may be very complex due to reflection and augmentation) to clinical CNS injury is also unclear, but ongoing efforts are well developed to computationally model all aspects of blast-associated phenomenon in virtual test facilities with bio-fidelic head models [54]. This approach has been extended with evaluation of personal protective equipment and the interaction with blast waves [55]. In particular, the virtual test environment allowed the development of an animal-to-human scaling law for blast-induced TBI assessment. This work was performed using experimentally validated blast

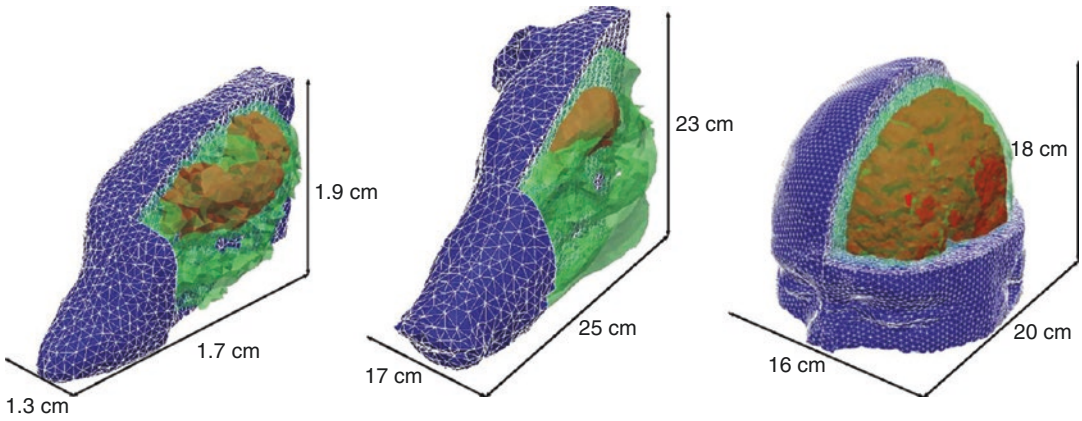

Fig. 8 Image-based finite element models of the head of mouse, pig, and human (not to scale) used in simulations, depicting the relevant tissue structures: skull (green), brain (red), and flesh (blue). (Source: Jeana et al. [56]. Open Access)

code and bio-fidelic models of the mouse, pig, and human skulls and intracranial tissue allowing development of a direct interspecies scaling law for blast exposure (Fig. 8). Human vulnerability to blast exposure was found to exceed that of other species, probably related to the relative mass of soft and bony tissue in other species compared to man [56]. One clinical aspect that has been noted in relation to blast-associated CNS injury is the increase in traumatic cerebral vasospasm, particularly in the setting of penetrating head injury [57].

The peak overpressure is most simply dependent on the distance from the blast source but approximately scales according to the standoff distance divided by the cube root of the explosive weight (Hopkinson Rule). The coupling of the nonlinear blast wave into biological tissue results in increased energy transmission at high strain rates in fractions of microseconds. The biological effect will depend on the constitutive tissue properties together with the largely unknown high strain rate of tissue material properties for brain. Ongoing research is establishing brain material properties across the strain-rate domain from low strain rates seen in impact injury to intermediate and higher strain rates seen in ballistic and blast injury. The above concepts lead to a frame of reference debate in relation to blast-induced military concussion or mTBI where it should be possible to rapidly approximate the potential exposure from any particular event to first-order accuracy.

Explosive detonation results in the formation of a detonation wave of altering chemical composition with the rapid formation of a propagated, nonlinear shockwave representing a large discontinuous increase in pressure, temperature, and density in the gas flow. The propagation of the shockwave develops a 3D complex fluid flow field that is altered by ambient conditions and environmental boundaries. This may result in multiple wave reflections and, potentially, pressure field intensification up to eightfold.

The blast waveform can be regarded as a combination of compressive and tensile components that impose a stress on the tissue in a manner that is dependent on the strain rate together with the constitutive properties of the tissue. This – combined with the potential for CNS injury from ballistic fragment acceleration-deceleration impact injury as well as chemical, thermal, and electromagnetic radiation – results in a highly complex problem where dominating effects become very difficult to parse in terms of their biological effects on the CNS.

Overlap of Wartime TBI and Acute Stress Disorders

The effect of military concussion and the development of persistent post-concussion symptoms together with other comorbidities, such as post-traumatic stress disorder (PTSD) (Fig. 9) and

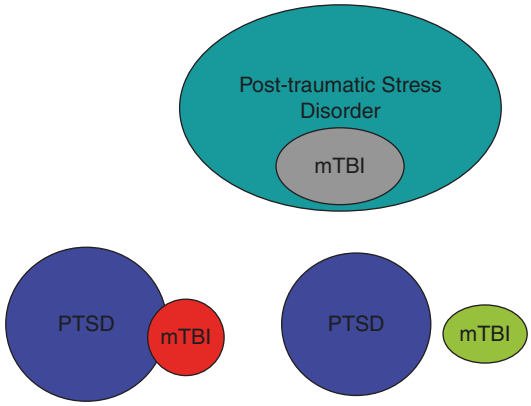

Fig. 9 Overlap of military concussion models and PTSD. The Venn diagrams represent various disease models of military mTBI and PTSD where military mTBI/concussion is regarded as a subset of PTSD to where the two disorders are regarded as independent (separated circles). Clinical perceptions suggest that the two disorder overlap to a greater and lesser degree within any clinical evaluation

depression, is an area of active research [58, 59]. Current studies are cross-sectional in design and may not have accounted accurately for statistical use of structural equation type of models. Further preliminary data from DTI suggest differences in blast(+)-exposed service members compared to non-blast-exposed service members in relation to such metrics as the FA, MD, and radial diffusivity.

Conclusions

TBI has been reported for centuries. Even until recently the serious nature of head injuries was minimized. For a long time, it was believed that woodpeckers could not develop tau pathology as seen in CTE. This has now been shown to be untrue. Blast-associated injuries and symptoms are only manifesting when there are distinct cognitive and functional difficulties, yet these may eventually be proven to be equally detrimental.

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Neuroradiological Imaging of Traumatic Brain Injury

Tuong Huu Le, Alisa Gean, and Shirley I. Stiver

Introduction

Traumatic brain injury (TBI) refers to injury to the intracranial structures following physical trauma to the head. TBI can be classified into *primary* and *secondary* injuries. Primary injuries are the result of direct trauma to the head and occur at the moment of impact. Secondary injuries arise as sequelae, due to activation of excitotoxic, oxidative, inflammatory, and other signaling cascades, following the primary injury. Secondary injuries are potentially preventable and treatable, whereas primary injuries, by definition, have already occurred by the time the patient first presents for medical attention. TBI can be further divided according to *location* (intra-axial or extra-axial) and also by the nature of the *mechanism* of injury (penetrating/open or blunt/closed). The severity of TBI is classified clinically according to the universally accepted Glasgow Coma Scale (GCS). Patients presenting with GCS < = 8 are designated as having a severe TBI, those with GCS between 9 and 12 are categorized as moderate injuries, and mild TBI (mTBI) encompasses patients with a GCS 13–15 [1]. From the moment of impact, TBI is a dynamic process with varying therapeutic windows, and early diagnosis and intervention are imperative for favorable outcomes.

Diagnosis and management of TBI requires a multidisciplinary approach, starting with a history and physical examination, followed by appropriate diagnostic imaging, and subsequent medical and/or surgical intervention as deemed necessary. The goals of imaging include identification of treatable injuries, recognition of sources of potential secondary damage, and analyses of factors that may provide useful prognostic information for long-term outcome. Advances in medical imaging technology have resulted in an explosion of novel imaging modalities that have improved the sensitivity and specificity for early detection of TBI and added a host of valuable prognostic indicators and signs to help guide patient management. Consequently, clinicians are faced with the difficult task of selecting the most appropriate diagnostic test from an array of available imaging techniques [2]. These decisions are of vital importance for optimal management, especially for injuries that require aggressive and timely intervention. This chapter reviews established methodologies and recent advances in imaging techniques together with selection paradigms for their application in the diagnosis of TBI. Characteristic imaging findings for individual TBI lesions will be described in

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detail, including a discussion of the unique imaging features of blast-induced brain injury.

Imaging Selections

Conventional Radiography

Conventional radiography itself (film or digital) is not sensitive for detection of intracranial pathology and should not be performed to evaluate parenchymal damage in TBI [3–5]. Patients who are at risk for acute intracranial injury should be imaged by computed tomography (CT). Skull radiographs may still be useful in a number of trauma settings. Plain skull films may assist in screening for head trauma in young children and infants. CT imaging imparts radiation exposure, and concerns of the long-term cancer risks of this procedure have been raised, especially in the younger population. Protocols to reduce radiation exposure for children undergoing CT imaging have helped to mitigate this risk [6]. Following trauma, children may seem invincible, often with no detectable abnormalities despite having incurred events with significant contact forces to the head. Given the frequency with which children fend off head trauma, CT imaging after each these events could contribute to significant radiation exposure risk. Plain skull films in young childhood head trauma can, with relatively little radiation exposure, screen for a skull fracture. This may be most helpful in young children less than 2 years in whom it may be difficult to elicit symptoms of headache or other complaints. A rule to guide screening for detection of a skull fracture in infants and young children includes the presence of a parietal or occipital swelling or hematoma and age less than 2 months, with sensitivity of 89% and specificity of 87% for detection of a fracture [7]. Skull fracture, with or without signs of neurological injury, is an independent risk factor for a neurosurgically relevant intracranial lesion [8]. Therefore, in the setting of clinically occult TBI, the diagnosis of skull fracture serves to alert the clinician to the possibility of an immediate or delayed neurologically relevant intracranial lesion. Nondepressed, linear fractures can be missed on CT imaging, especially if the plane of the imaging slices lies parallel to the fracture [9]. Review of the scout image can often reveal fractures hidden on axial images. However, the poor resolution and single view afforded by the scout image may still miss and confound the diagnosis of many simple skull fractures. Skull films, typically with anterior-posterior and lateral views, enable better visualization of the extent of skull fractures and of entrance and exit skull defects in penetrating head injury.

Computed Tomography

CT is the primary modality of choice for evaluating head trauma because it is fast and widely accessible, and there are few contraindications to a non-contrast CT scan. Pregnancy, especially in the first trimester, is a relative contraindication for a CT scan. However, in the setting of major trauma, the priority is stabilization and care of the mother [10]. It has been recommended that even a CT of the abdomen to evaluate blunt or penetrating trauma to the abdomen of the mother should not be delayed or deferred because of radiation exposure concerns [10, 11]. Fetal head trauma has been recognized by skull radiography in a few cases of blunt abdominal trauma in pregnant trauma patients [12–15]. Especially in the second and third trimesters, the risk of radiation exposure to the fetus is minor when balanced against the potential benefits of imaging to evaluate the presence and extent of maternal or fetal injury [10, 11]. The risks of ionizing radiation are more significant in infants and children, and protocols which entail lower radiation exposure are recommended in the CT imaging of these patients [16]. In the setting of TBI, one needs to balance the risks of the CT against how the information from the scan might alter the patient's management. Unlike magnetic resonance imaging (MRI), CT can easily accommodate life support and monitoring equipment. In addition, CT is superior to MRI for the detection of skull fractures and radio-opaque foreign bodies. MRI is

contraindicated in the presence of certain ferromagnetic foreign bodies.

In the setting of acute head trauma, a non-contrast CT is recommended for patients with moderate and severe TBI (GCS ≤ 12) and in any patient with evidence of a penetrating injury. For patients with mTBI (GCS > 12), the New Orleans Criteria (Box 1) [17], the Canadian CT Head Rule (Box 2) [18–20], and the National Emergency X-Ray Utilization Study (Nexus-II) (Box 3) [21] can guide whether a CT scan should be performed. While there is some variability among these guidelines, together they suggest that older age, altered level of consciousness, persistent neurologic deficit(s), vomiting, significant skull fracture, and bleeding diathesis or anticoagulation therapy are factors advocating for CT imaging of a mTBI patient [17–20, 22–25]. Similar guidelines have been published by the Pediatric Emergency Care Applied Research Network (PECARN) for the pediatric population [26]. Non-contrast CT scans provide rapid and accurate detection of space-occupying hematomas and associated mass effect. The value of repeat CT imaging to change clinical management is considered to be low in the absence of an observed neurological change or high-risk features, characterized as sub-frontal or temporal contusions, anticoagulation, age over 65 years, or intracranial hematoma of volume greater than 10 ml [2, 27–31].

Box 1 New Orleans Criteria for mTBI: A non-contrast CT of the head is indicated if the patient meets one or more of the following criteria

Headache
Vomiting
Age > 60 years
Drug or alcohol intoxication
Persistent antegrade amnesia (short-term memory deficits)
Visible trauma above the clavicle
Seizure

Data from Haydel et al. [17]

Box 2 Canadian CT Head Rule for mTBI: A non-contrast CT of the head is indicated if the patient meets one or more of the following criteria

GCS < 15 2 hours after injury
Suspected open or depressed skull fracture
Any sign of basal skull fracture
Two or more episodes of vomiting
Age ≥ 65 years
Amnesia before impact of 30 min or more
Dangerous mechanism (i.e., pedestrian struck by motor vehicle, occupant ejected from motor vehicle, or a fall from a height of at least 3 ft or five stairs)

Data from Stiell et al. [18–20]

Box 3 NEXUS-II: CT imaging is not necessary in the absence of all of the following criteria

Age above 65 years
Skull fracture
Scalp hematoma
Neurological deficit
Altered level of consciousness
Abnormal behavior
Coagulopathy

Data from Mower et al. [21]

Intravenous contrast should not be administered before a baseline non-contrast CT has been performed, because the contrast can both mask and mimic underlying hemorrhage. A contrast CT after the non-contrast scan can, however, be very informative in detecting signs of active extravasation and alerting the clinician to a highly unstable lesion that has risk for rapid enlargement. In the trauma setting, adverse reaction to contrast agents, additional radiation exposure, and time constraints typically disfavor a contrast CT as a routine procedure. Contrast CT scans are, however, often obtained as adjuncts to CT angiography (CTA) or CT perfusion imaging studies.

CT angiography (CTA) and CT venography (CTV) utilize iodinated intravenous contrast to delineate the vascular structures at high

(submillimeter) resolution. CTA is best performed with multi-detector CT (MDCT) and rapid bolus contrast injection using a vessel tracking technique. Typical imaging parameters include a slice thickness of 1.25 mm, with a 0.625 mm overlap, and a bolus injection rate between 3 and 4 mL/s. Suspicion for a fracture traversing the path of a major artery or venous sinus is a common basis to perform a CTA or CTV study to evaluate the occurrence of significant vascular injury, such as a dissection, fistula, stenosis, or occlusion [32]. Traumatic vascular injuries can occur even if the fracture is not displaced. In many situations, with the exception of penetrating injury with retained ferromagnetic foreign fragments, MR arteriography (MRA) and MR venography can also be used to delineate these vascular injuries. The choice between CT and MR vascular imaging modalities depends on a number of factors, including time constraints, the likelihood that fracture artifact may confound interpretation of a vascular injury, the stability of the patient to undergo MR scanning, radiation exposure, and the possible need for ongoing surveillance imaging.

Xenon CT incorporates patient inhalation of an approximately 70:30 mixture of oxygen and nonradioactive xenon-131 during a CT scan. The xenon gas is highly lipid soluble and readily crosses the blood-brain barrier. Xenon CT has been used to evaluate cerebral blood flow (CBF) in TBI patients, with isolated reports further exploring how CBF measurements at different carbon dioxide levels and cerebral perfusion levels can be used to study perturbations in cerebral autoregulation and carbon dioxide reactivity [33, 34]. In traumatic contusion injuries, xenon CT has demonstrated that CBF is depressed in a concentric manner about the epicenter of contusions [35]. Quantitative xenon CT measurements of CBF obtained within 12 hours to 3 days following severe TBI have been shown to correlate with outcome, as assessed by the Glasgow Outcome Score (GOS) at 3, 6, and 12 months following injury [36, 37]. Similarly, global and lobar CBF measurements by xenon CT, at varying points across all grades of TBI, demonstrated that both measures correlated with GOS [38]. In a longitudinal study, serial CBF measurements obtained weekly for the first 6 weeks post-injury were analyzed in reference to neurological outcome at 6 months [39]. Outcome following severe TBI was better for those in whom low CBF had normalized by 2–3 weeks following injury, as compared to those with persistently low CBF beyond 3 weeks. The disadvantages of xenon CT imaging include radiation exposure, mild adverse effects on respiration or the sensorium, and a small (estimated to be less than 5%) augmentation of CBF induced by the xenon gas [40, 41].

Perfusion CT measures several indices of brain hemodynamics by tracking transient attenuation changes in the blood vessels and brain parenchyma during the first pass of an intravenously injected contrast bolus [42]. In contrast to PET and xenon CT, which employ diffusible tracers, CT perfusion imaging uses an intravascular tracer. Perfusion CT involves continuous cine scanning with a scan interval of 1 s and a total scanning duration of 40–45 s [43]. Algorithms are often employed to correct for variations in the time for the contrast bolus to reach each tissue voxel of interest [44]. Computer deconvolution generates a tissue residue function, a measure of the contrast remaining in a voxel over time. Color-coded maps of cerebral blood volume (CBV), mean transit time (MTT), and cerebral blood flow (CBF) are generated from a voxel-by-voxel analysis of the tissue residue function [44]. CBF is considered the best measure of how well the brain tissue is perfused, while MTT represents the average time of contrast transit and includes a measure of the time for the contrast to travel from an artery to the tissue. CBV, determined from the mathematical relationship CBF=CBV/MTT, represents the vascular volume containing contrast within a voxel and is a useful measure of the area of an infarct. In severe head injury patients, evidence of normal perfusion or hyperemia on CT perfusion imaging has been shown to correlate with favorable outcome, while findings of oligemia have been associated with unfavorable outcome [45]. One limitation of CT perfusion is the additional radiation exposure that accompanies cine imaging.

Magnetic Resonance Imaging

Conventional MRI

MRI may be indicated in patients with acute TBI if the neurologic findings are unexplained by the CT imaging. Routine MR imaging for TBI typically includes T1- and T2-weighted spin-echo, gradient-echo, and inversion recovery MR sequences. In subacute and chronic TBI, MRI is often preferred over CT because of its superior sensitivity to both detect and date older blood products. Compared to CT, MRI is more sensitive for detection of subtle extra-axial "smear" (i.e., very thin layer) hematoma collections. Fluid-attenuated inversion recovery (FLAIR) MRI can also be more sensitive to subarachnoid hemorrhage [46, 47]. MR is extremely useful for the detection of traumatic axonal shear injury (TAI). Typically small and often localized to the brainstem, CT is often unable to detect these lesions. TAI lesions may be accompanied by microscopic hemorrhage, which increases the sensitivity of MRI to detect these lesions using gradient-echo sequences. Gradient-echo sequences in the coronal plane are particularly useful for identifying shear injury in the temporal stem, posterior corpus callosum, and brainstem. The burden of traumatic axonal shear injury, especially in the brainstem, can help guide outcome prognostication for deeply comatose patients.

Fluid-attenuated inversion recovery (FLAIR) imaging suppresses the bright cerebrospinal fluid (CSF) signal typically seen on conventional T2-weighted images, thereby improving the ability to discriminate focal cortical injuries, white matter shearing injuries, and subarachnoid hemorrhages. Sagittal and coronal FLAIR images are particularly helpful in the detection of TAI involving the corpus callosum and the fornix, two areas that can be difficult to evaluate on routine T2-weighted images [48]. Abnormal high signal in the sulci and cisterns of ventilated patients receiving a high inspired oxygen fraction greater than 0.60 (inspired oxygen fraction = [flow $\text{rate}_{\text{air}} \times 0.21$ + flow $\text{rate}_{\text{oxygen}}$]/[flow rate_{air} + flow $\text{rate}_{\text{oxygen}}$ + flow $\text{rate}_{\text{nitrous oxide}}$]) can be observed on FLAIR sequences in normal, uninjured patients and should not be mistaken for subarachnoid hemorrhage [49, 50].

Gradient-recalled echo (typically referred to as gradient-echo) (GRE) T2∗-weighted imaging is highly sensitive to the susceptibility changes among tissues. The presence of blood breakdown products from brain injury, such as methemoglobin, ferritin, and hemosiderin, alters the local magnetic susceptibility of tissue, resulting in areas of signal loss on GRE T2∗-weighted images. Because hemosiderin can persist indefinitely, its detection on GRE T2∗-weighted images is especially useful for the evaluation of remote TBI. Small foci of hemosiderin can, however, sometimes be resorbed; therefore, the lack of hemosiderin on GRE T2∗-weighted images does not rigorously exclude old hemorrhage [51].

Advanced MRI Methods

Susceptibility-weighted imaging (SWI) further amplifies the susceptibility changes among tissues and blood products by combining magnitude and phase information from a high-resolution, velocity-compensated 3D T2∗-weighted gradient-echo sequence [52, 53]. Conventional GRE T2∗-weighted MRI relies only on the magnitude images and ignores the phase images, the latter of which contain valuable information regarding tissue susceptibility differences. In SWI, phase images are unwrapped and high-pass filtered to highlight phase changes. These are then converted to "mask" images that are multiplied with information from the corresponding magnitude images. The tissue magnetic susceptibility contrast afforded by SWI is significantly enhanced for the detection of small hemorrhages. SWI is three to six times more sensitive than GRE T2∗-weighted imaging for detection of hemorrhagic TAI [54–56].

Diffusion-weighted imaging (DWI) measures the random microscopic motion of water molecules in brain tissue. Two indices, the apparent diffusion coefficient (ADC) and the fractional anisotropy (FA), are obtained from DWI imaging. ADC measures the magnitude of water diffusion averaged over a three-dimensional (3D) space. FA measures the preferential motion of water molecules in one direction typically, in its applications

to TBI, along white matter axons. DWI is very sensitive to alterations in the pattern of water molecule movement that occurs following acute shear injury. Thus, DWI has been particularly useful for the detection of TAI [57–61]. DWI identifies more acute TAI lesions than fast spin-echo T2-weighted and/or GRE T2∗-weighted images. Acute TAI lesions have been reported to be associated with reduced FA. However, not all studies have uniformly found this. For example, a meta-analysis of the DWI literature of TBI patients has reported that FA values are increased in the acute phases of TBI, within 14 days of injury, while the chronic phases of TBI are associated with reduced FA [62]. This study further suggested that poor neuropsychological outcome correlated with high anisotropy in the acute, and depressed anisotropy in the chronic, phases of TBI [62]. Considerable variances exist in the acquisition and interpretation of diffusion-weighted imaging, and further work is necessary to validate the routine use of DWI in TBI.

Diffusion tensor imaging (DTI) uses information acquired from DWI to analyze the rate and direction of diffusion of water molecules. The integrity of the white matter tracts can be mapped by DTI with 3D tractography [63, 64]. Images of the white matter fiber tracts are generated based on the direction of fastest diffusion of water molecules, which is assumed to correspond to the longitudinal axis of the fiber tract. DTI has been applied to the study of mTBI and concussion injuries [65–69]. Using 3T DTI, radial diffusivity in fibers of the corpus callosum projecting to prefrontal cortex has been observed to be depressed in concussed female athletes 6 months following injury [65]. A review of 10 DTI studies of patients with post-concussion syndrome following mTBI noted a decrease in FA in varying locations but most frequently in the corpus callosum [66]. In this review, differences in FA were observed in studies that used a ROI analysis, while two studies that employed a voxel-wise analysis failed to detect significant changes in FA. Abnormalities identified within the white matter tracts created with DTI need to be carefully assessed for the parameters, technical expertise, and reproducibility of the image processing to distinguish true lesions from artifacts. One limitation of routine DTI is that it assumes a one-fiber model for each voxel and does not have the resolution to account for crossing white matter tracks within a voxel. Advanced diffusion MRI with high-spatial and angular techniques provide high-resolution tractography images capable of differentiating closely approximated and crossing tracts [70–72]. At present, the reticular formation and associated tracts cannot be reliably mapped by these techniques [70]. However, further advances in the ability to map lesions, such as TAI in the white matter tracts of the brainstem, may possibly enable the assessment of brainstem lesions in patients with vegetative and minimally conscious states.

MR spectroscopy (MRS) allows for in vivo measurement of the relative amounts of metabolites in brain tissue. Common brain metabolites that are measured with proton (^{1}H) MRS include *N*-acetylaspartate (NAA), creatine (Cr), choline (Cho), glutamate, lactate, and myoinositol [73]. NAA is a cellular amino acid and is a marker of neuronal health. Creatine is a marker of energy metabolism and cellular density. Creatine is especially abundant in glial cells and can serve as a marker for post-traumatic gliosis. Cho is a marker for membrane disruption, synthesis, or repair. An increase in Cho is observed in myelin injury. Choline metabolites may be released as a result of myelin damage following TBI [74]. MRS can detect abnormalities that may not be visible on conventional MRI [75, 76]. A number of studies have correlated decreases in NAA and elevations in Cho with injury severity and outcomes following TBI [73, 75, 77–79]. Many MRS studies quantify changes in the metabolite of interest relative to Cr as an internal standard. Of note, Cr concentrations have been observed to be altered by mTBI, suggesting that metabolite ratio measurements referenced to Cr may be somewhat unreliable [80, 81].

Changes in NAA studied over time following mTBI have been shown to correlate with the dynamic nature of recovery after head injury. In a study of 40 athletes with concussion injuries, initial decrements in NAA measured at day 3 after injury slowly improved to day 15 and then more quickly returned to normal by 30 days post-injury

[82]. Interestingly, concussive symptoms cleared between days 3 and 15, seemingly in keeping with the temporal profile of changes in NAA [82]. A longitudinal study of 17 mTBI patients similarly reported recovery of metabolic changes following TBI, although in this study normalization took 3–5 months [81]. This study included analysis of glutamine and glutamate neurometabolites, markers of excitotoxicity following TBI. The study noted significant difference in the patterns of metabolic changes between mild and severe TBI. In mTBI, subtle changes in Cr and glutamine/glutamate were found in the white matter, while changes in NAA and Cho metabolites were prominent in severe TBI. These differences may suggest that mild and severe TBI may be two distinct forms of injury [81]. Mild, moderate, and severe TBI brings about changes in brain metabolism, and MRS holds promise as a technique to investigate injured brain tissue that may appear normal on conventional imaging studies.

Magnetization transfer imaging (MTI) exploits the longitudinal (T1) relaxation coupling between bound (hydration) protons and free water (bulk) protons. In MTI, protons that bind to macromolecules are selectively saturated using an off-resonance saturation (radiofrequency) pulse. These bound protons then exchange longitudinal magnetization with free water protons. This magnetization transfer leads to a reduction in signal intensity from the free protons. The magnetization transfer ratio (MTR), a relative measure of the reduction in signal intensity due to the magnetization transfer (MT) effect, provides a quantitative measure of the structural integrity of the tissue. MTI has been applied to study the integrity of white matter that otherwise appears normal on routine MR imaging. MTR evaluations of 28 TBI patients demonstrated abnormal MTR values in all 8 patients with persistent neurological deficits [83]. In a study of 30 TBI patients, MTR assessments at a median of 41 days after injury showed abnormal MTR values in 2 of the 10 patients with a poor outcome, a GOS of 1–4 [77]. In mTBI patients, 2 of 13 were found to have MTR values two standard deviations below controls, which correlated with poor neuropsychological test results [84]. Statistical reductions in MTR have been found even 3 years after injury in moderate and severe TBI [85]. Currently, MTI is an investigational adjunct to the study of TBI.

Perfusion MRI employs either dynamic susceptibility contrast (DSC) or arterial spin labeling (ASL) imaging. In DSC-MRI, following intravenous injection of gadolinium contrast, continuous cine imaging of fast (echo-planar) T2∗-weighted images is performed. As the contrast passes through the tissues, it causes susceptibility changes and associated reduction of signal intensity on T2∗-weighted images. Maps of CBF, CBV, and MTT can be generated using pixel-by-pixel analysis of the signal changes. Importantly, the signal intensities measured using DSC-MRI are not linearly proportional to the concentration of gadolinium. Thus, perfusion parameters obtained using DSC are only qualitative comparisons between the two hemispheres [44]. By comparison, ASL-MRI does not employ administration of gadolinium contrast. ASL-MRI is a noninvasive method to measure CBF by using the water molecules in arterial blood as a natural diffusible tracer. With ASL-MRI, protons of water molecules in inflowing arterial blood are "labeled" using radiofrequency (inversion or saturation) pulses proximal to the tissue of interest. Images of the tissue of interest are acquired after a short delay (usually 1 s) that allows time for the spin-labeled water in the blood to flow into the imaging slices. The perfusion parameters are calculated by pair-wise comparison with baseline control images acquired without spin labeling. Based on the half-life of the T1 relaxation time for protons of water molecules in blood, relative measures of CBF can be quantified. Contrast is not administered, and, therefore, ASL scans can be repeated as often as necessary during the same scanning session. As for CT perfusion, MR perfusion studies provide valuable assessments of the response of the vasculature to TBI.

Magnetic Source Imaging

Magnetic source imaging (MSI) utilizes magnetoencephalography (MEG) to localize weak mag-

netic signals that are generated by neuronal electrical activity. Electrical currents flowing within dendrites give rise to a surrounding magnetic field that can be measured by superconducting quantum interfering devices (SQUID). MEG selectively measures activity in dendrites oriented parallel to the skull surface. MSI integrates anatomic data obtained by conventional MRI with electrophysiological data obtained by MEG. MSI studies have demonstrated abnormal low-frequency magnetic activity in mTBI patients with post-concussive syndrome [86, 87]. Integration of MEG with DTI detected abnormal findings in 9 of 10 mTBI patients in whom conventional CT and MR imaging was normal [88]. Progress in MEG imaging techniques has enabled more robust and automated evaluation of mild and moderate TBI in both blast and non-blast injuries [89]. MSI is a promising imaging modality for the assessment of TBI, although further research is warranted before MSI is routinely used in the clinical setting.

Positron Emission Tomography

Positron emission tomography (PET) utilizes positron-emitting isotopes, commonly 15-oxygen (^{15}O) to measure cerebral perfusion and oxygen metabolism and 2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) to measure cerebral glucose metabolism. The radioisotopes used in PET imaging are produced by a cyclotron and have a short half-life, generally necessitating use within a day. PET enables regional maps detailing the quantitative in vivo assessment of CBF and metabolic changes following TBI. ^{15}O-PET measurements within 24 hours of injury in 15 moderate and severe TBI patients found, in comparison to healthy controls, significant decrements in CBF and cerebral metabolic rate of oxygen (CMRO2) and increases in oxygen extraction fraction (OEF) [90, 91]. OEF measurements were used to calculate the volume of ischemic brain, a measure of the burden of ischemic injury. The volume of ischemic brain was significantly increased within 24 hours of TBI and correlated with outcome assessed by GOS at 6 months following injury [90, 91].

^{18}F-FDG can evaluate glucose metabolism, a surrogate marker of neuronal injury, following TBI [92]. Acutely injured brain cells show increased glucose metabolism following severe TBI due to intracellular ionic perturbation [93, 94]. Following this initial hyperglycolysis state, a prolonged period of regional hypometabolism then ensues. Since glucose metabolism reflects neuronal activity, regional hypometabolism implies neuronal dysfunction. Thus, ^{18}F-FDG is considered a surrogate marker of the functioning of injured neurons and has the potential to reveal cerebral dysfunction in regions that would appear otherwise "normal" on CT or MRI [95–97]. More sophisticated PET imaging techniques incorporate specific ligands allowing for the evaluation TBI at the molecular level. For example, using a carbon 11-labeled ligand for amyloid, PET imaging has demonstrated an increase in amyloid in the cortical gray matter and striatum in TBI patients [98]. PET imaging of retired professional football players using [F-18]FDDNP, a fluoro-18 ligand with a high affinity for tau, has demonstrated increased signal in patterns consistent with tau immunohistochemistry studies of autopsy specimens of chronic traumatic encephalopathy (CTE) and distinct from the patterns of tau deposition seen in Alzheimer's disease [99, 100]. PET is still relatively expensive and is not widely available for the evaluation of TBI.

Single-Photon Emission Computed Tomography

Single-photon emission computed tomography (SPECT) is similar to PET, employing radioactive isotopes to detect gamma rays. Technetium-99 is a common isotope used in SPECT. SPECT images are lower resolution than those in PET, but the isotopes used are more easily produced and have a longer half-life. They cross the blood-brain barrier into the brain parenchyma, and radiotracer measurements can be used to semi-quantitatively determine CBF. A review of 19 longitudinal and 52 cross-sectional SPECT imaging studies for TBI addressed questions of lesion detection, relationship to neuropsychological

testing, and applications to treatment interventions [101]. SPECT imaging was able to identify areas of perfusion abnormality in patients with head trauma and "normal" CT and MRI studies [101, 102]. Abnormalities were commonly found in the frontal, as well as temporal, lobes [101]. However, due to its low spatial resolution, SPECT is limited in its ability to detect small perfusion defects in lesions that are visible on CT or MRI. Treatment studies including cognitive behavioral therapy, hyperbaric oxygen therapy, and alternative dietary and lifestyle changes have demonstrated correlations between improvements in neuropsychological tests and improved cerebral blood flow on SPECT imaging [103–106].

Imaging Findings

Missile and Penetrating Injury

In the United States, the majority of *missile and penetrating injuries* are due to assaults and suicide attempts [107]. Unfortunately, penetrating injuries as the result of war and acts of extreme violence are being seen more frequently in veterans returning from conflicts overseas, as well as in civilian victims [108]. More than 80% of gunshot wounds to the head penetrate the scalp and skull. Missile injuries result in various forms of brain damage, depending on the mass, velocity, and shape of the missile. Missile injury is classified as superficial, depressed, penetrating, or perforating. In *superficial missile injury*, the missile remains extracranial, and the skull is intact. However, significant brain damage can still occur, as the force of the initial impact can be transmitted to the underlying brain tissue (Fig. 1a, b). Even superficial, small shotgun fragments can cause intracranial injury because they are often of high velocity. The applied energy and, therefore, the tissue damage incurred depend not only on the mass (m) of the missile but also on the square of its velocity (v) (i.e., kinetic energy = ½ mv^2). With increases in velocity, an extracranial missile may have enough impact to cause a depressed skull fracture and subjacent parenchymal injury, resulting in a *depressed missile injury* (Fig. 2a, b). However, the majority of ballistics penetrates the skull, meninges, and brain, causing a *penetrating missile injury*. The brain laceration caused

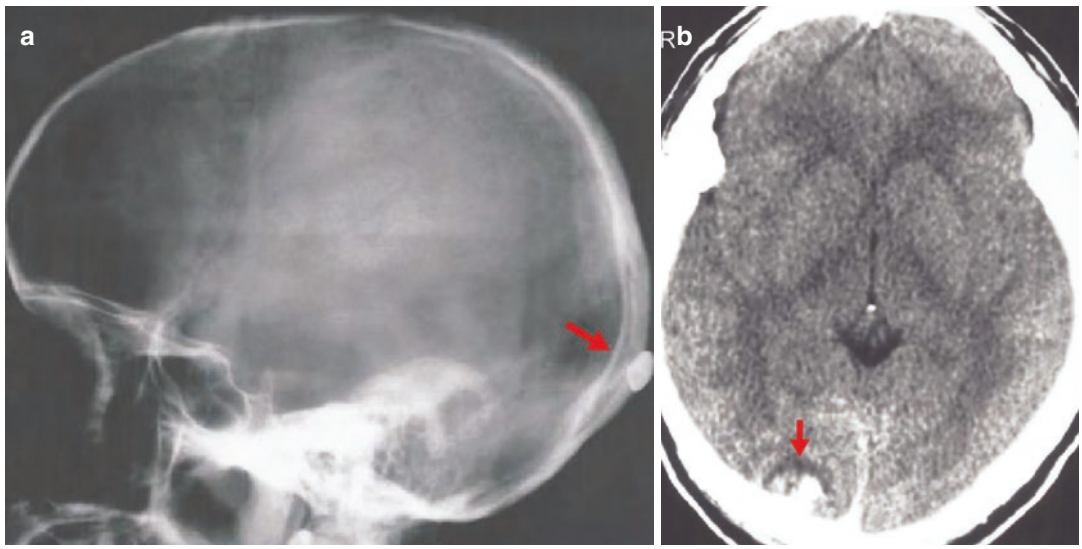


Fig. 1 Superficial missile injury. (**a**) Lateral skull film shows a bullet lodged within the soft tissue overlying the occiput. (**b**) Non-contrast axial CT, performed after removal of the bullet, demonstrates a subjacent left occipital lobe contusion (*arrow*). No fracture is identified on the "bone window" images (not shown). (Both: Reprinted with permission of Wolters Kluwer from Gean [145])

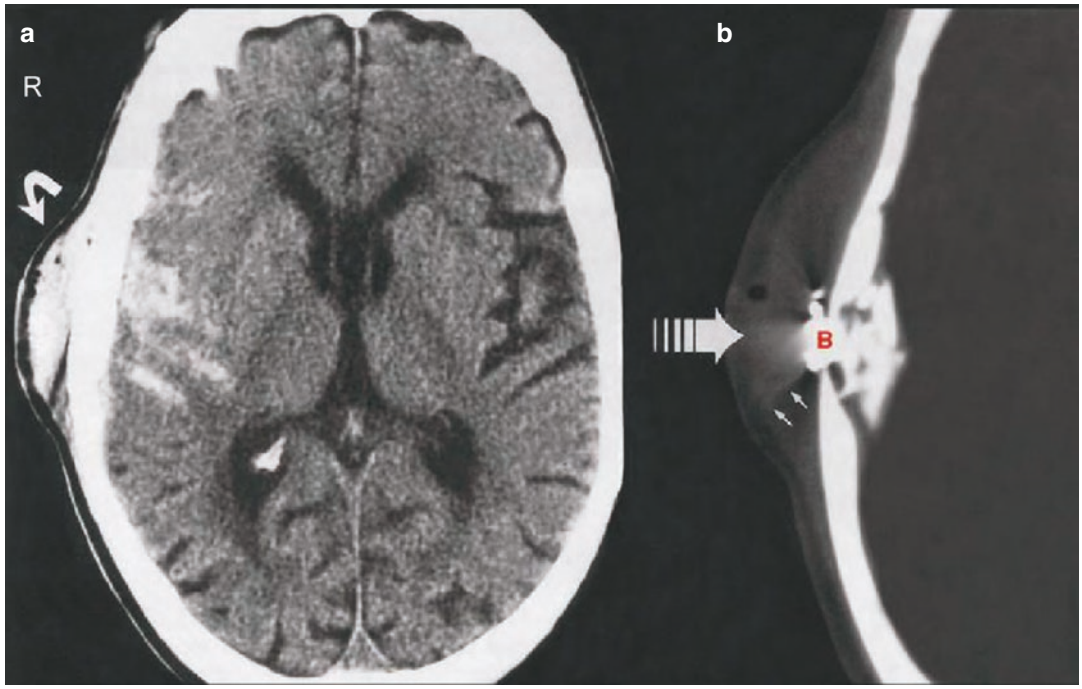


Fig. 2 Depressed missile injury. (**a**) Non-contrast axial CT image demonstrates posterior right temporal scalp soft tissue swelling (*curved arrow*) and a subjacent temporal contusion, subarachnoid hemorrhage, and effacement of the frontotemporal sulci. (**b**) CT image displayed in bone window reveals a bullet fragment (B) lodged within the outer table of the skull. Multiple bone fragments from the inner table of the skull are noted. (Both: Reprinted with permission of Wolters Kluwer from Gean [146])

by the missile is characteristically canalicular, with decreasing diameter along its course through the brain. In addition to tissue damage along its trajectory, damage may arise from shock waves emanating from the passage of the missile. A high-velocity missile can generate enough shock wave damage to cause a contusion at a distance from the missile trajectory or even result in diffuse cerebral edema (Fig. 3a, b). After traversing through the brain parenchyma, missiles may ricochet off the inner table of the skull and create further damage along a second trajectory. Ricochet of missiles creates widespread brain damage. With even greater velocity, a missile can exit the contralateral side of the skull, resulting in a *perforating missile injury*. The skull defect at the exit site is usually larger than that at the entry site [108]. The entry and exit sites of a penetrating injury may be distinguished by characteristic beveling patterns at each site. The inner table of the skull is beveled at the entry site, while the outer table of the skull is beveled at the exit site (Fig. 4a–f).

In evaluating imaging studies of patients with missile injuries, the radiologist should be aware of the imaging features of retained unexploded ordnances (UXOs). UXOs are ballistics designed to explode upon impact. The most well-known example of a UXO is the devastator bullet that failed to explode during the attempted assassination of President Ronald Reagan [109]. Given the complexities of their design, UXOs may fail to detonate upon striking their victim; however, they continue to have explosive potential, putting both the victim and health-care providers at risk. Careful precautions are required, as detonation can be triggered by pressure, heat, static electricity, and other seemingly routine events [110]. Factors, including the circumstances leading to the injury, are used to evaluate the risk that a retained missile may represent a UXO. In addition, UXOs have a number of design features that

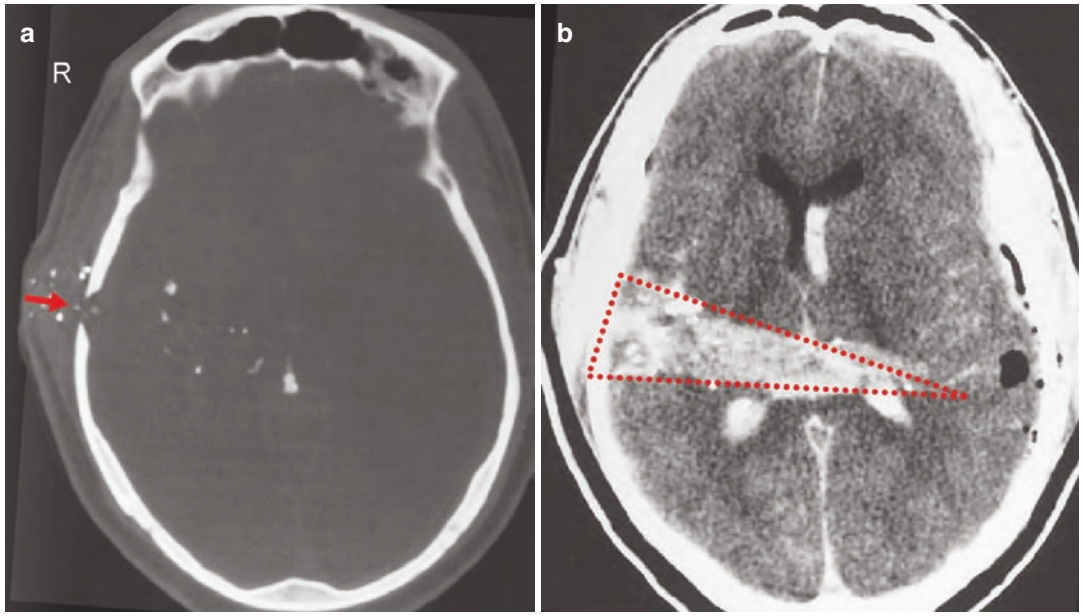


Fig. 3 Penetrating missile injury. (**a**) Axial CT bone window demonstrates the typical entry site of a penetrating gunshot wound (GSW). Note beveling of the inner table of the skull (*arrow*). (**b**) CT slice slightly more superior and displayed at brain windows shows hemorrhage along the path of the bullet, with scattered bone and bullet fragments along the trajectory. There is intraventricular, subarachnoid, and subdural hemorrhage present as well as a small amount of pneumocephalus. Note especially the characteristic cone-shaped wound canal at the base of the entry site (*red triangle*). (Both: Reprinted with permission of Wolters Kluwer from Gean [149])

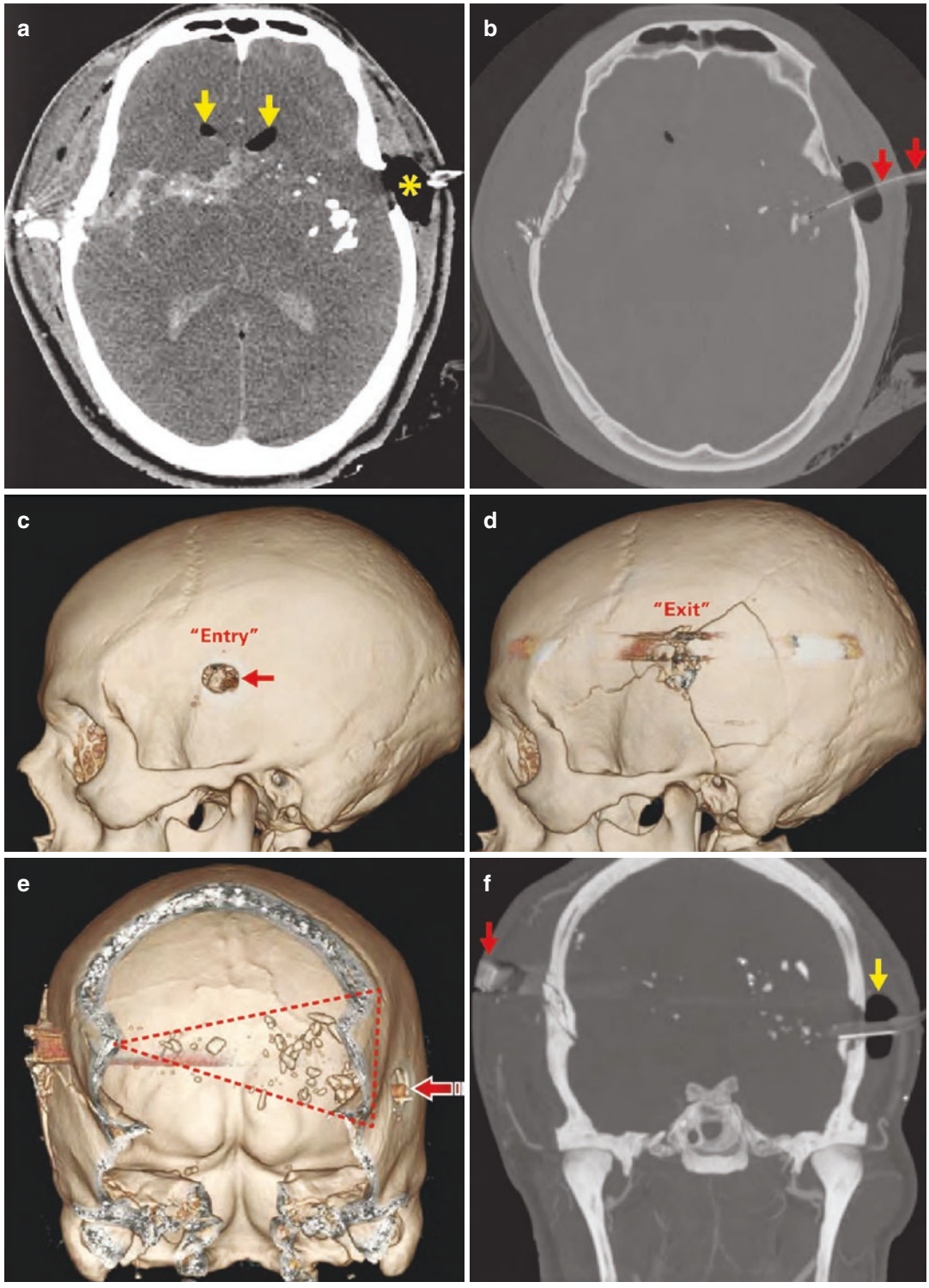
can be identified radiologically. Based on a few anecdotal cases, CT radiography and ultrasound are thought to be safe modalities for imaging patients who may harbor a UXO [110, 111]. If a patient is considered at risk for harboring a UXO, the patient should be moved carefully onto and off the CT scanning table. Scout views of CT imaging are particularly informative for the evaluation of a possible UXO. UXOs are generally large missiles. The caliber can be measured on the scout image, and a missile greater than 7.62 mm raises suspicion for a UXO [110]. In order to accommodate the explosive or flammable materials, UXOs often have a hollowed-out core. On the scout CT, identification of a central cylindrical hypodensity at the base of the projectile is typical of a UXO [110]. In other designs, the explosive and flammable materials of a UXO are embedded in the tip of the projectile giving rise to a distinct appearance on the scout image of alternating densities at the tip of the projectile [110]. Making the diagnosis of a retained UXO initiates a highly stressful situation, including the need to notify the US military [110]. The radiologist needs to evaluate the risk that a retained missile may represent a UXO very carefully and judiciously.

Blunt Injury

Primary Extra-axial Injury

Pneumocephalus

Pneumocephalus (intracranial air) following TBI indicates that a communication has formed between the intracranial and extracranial compartments. Pneumocephalus can occur in the epidural (Fig. 6), subdural, subarachnoid, or intraventricular space or in the brain parenchyma (pneumatocele). Traumatic fractures of the paranasal sinuses, together with a transient imbalance in the pressure gradient between the extracranial and intracranial compartments, set the stage for pneumocephalus. With a calvarial-dural defect, rapid increases in pressure within the paranasal


a
b
c
"Entry"
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f

Fig. 4 Perforating missile injury. (**a**) Axial CT image demonstrates multiple bone and bullet fragments traversing diagonally across the midline. There is diffuse cerebral edema and bifrontal intraventricular air (*arrows*). There is a drainage catheter (*asterisk*). (**b**) Bone window reveals characteristic beveling of the inner table of the skull at the entry site. The drainage catheter is noted (*arrows*). (**c, d**) Volume-rendered 3D CT images demonstrate the well-defined entry site (arrow) and the comminuted fractures at the exit site. This is a classic example of how a bullet punches out a circular wound at the entrance in the skull, driving fragments of bone into the brain. These bone chips create secondary tracks that deviate from the main path and destroy additional tissue. (**e**) Coronal 3D cutaway CT image demonstrates the left-to right trajectory of the GSW with innumerable fragments scattered throughout the brain, most of which are located toward the entry site (*arrow*). Note the cone-shaped distribution of intracranial fragments with the base of the cone centered at the entry site (*triangle*). (**f**) Coronal maximum intensity projection (MIP) image from the CTA shows many of the abovementioned findings, including the drainage catheter occluding the entry site (yellow arrow), beveling of the inner table of the skull, multiple bone fragments along the GSW trajectory, a comminuted fracture at the exit site, and the major ballistic fragment lodged within the right frontotemporal scalp soft tissues (*red arrow*). (All: Reprinted with permission of Wolters Kluwer from Gean [150])

sinuses (e.g., from sneezing or coughing) may force air into the intracranial cavity. Pneumocephalus may also arise from a compensatory influx of air in response to a decrease in intracranial pressure, as may occur from leakage of CSF, for example, following a traumatic fracture that breaches the dura. The most frequent cause of traumatic pneumocephalus is a fracture of the posterior wall of the frontal sinus. Pneumocephalus is easily detected on CT imaging due to the characteristic Hounsfield units (HU) of air. On imaging, epidural, subdural, or intraventricular collections of air usually accumulate ventrally since most patients are scanned in the supine position. Pneumocephalus may also appear as small collections of air dispersed throughout the subarachnoid space. Most cases of pneumocephalus resolve spontaneously. In rare instances, a ball-valve communication between the extracranial and intracranial compartments allows air to preferentially enter, but not exit, the intracranial cavity. This leads to tension pneumocephalus, an expanding collection of intracranial air under pressure. Tension pneumocephalus can cause headache, stiff neck, stupor, papilledema, and mass effect leading to cerebral herniation [112]. Tension pneumocephalus requires urgent intervention, usually with a burr hole or twist drill, to decompress the trapped air under pressure.

Epidural Hematoma

On CT imaging, traumatic *epidural hematomas* (EDH) are characteristic ovoid collections of blood situated beneath the inner table of the skull and above the dura. They are extradural lesions, and the brain parenchyma itself is not subjected to any form of direct traumatic hemorrhage. However, epidural hematomas often cause indirect brain injury, by exerting mass effect with focal compression of the underlying brain. The EDH is subperiosteal; it rarely crosses cranial sutures, where the outer periosteal layer of the dura is firmly attached at sutural margins (Fig. 5) [107]. At the vertex, however, where the periosteal dural layer is not tightly attached to the sagittal suture, an EDH can cross the midline.

EDHs are usually arterial in origin. Most EDHs occur at the coup site (i.e., the site of impact) in association with a skull fracture. They commonly occur in the temporal squamosa

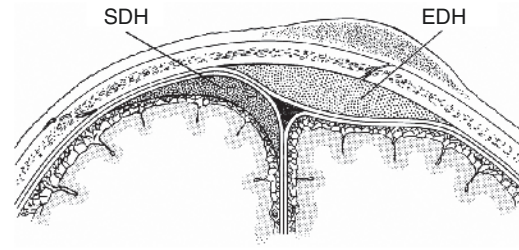

Fig. 5 Coronal diagram of the EDH and SDH. The EDH is located above the outer dural layer (i.e., the periosteum), and the SDH is located beneath the inner (meningeal) dural layer. The EDH does not cross sutures. The SDH does not directly cross the falx or the tentorium. (Reprinted with permission of Wolters Kluwer from Gean [147])

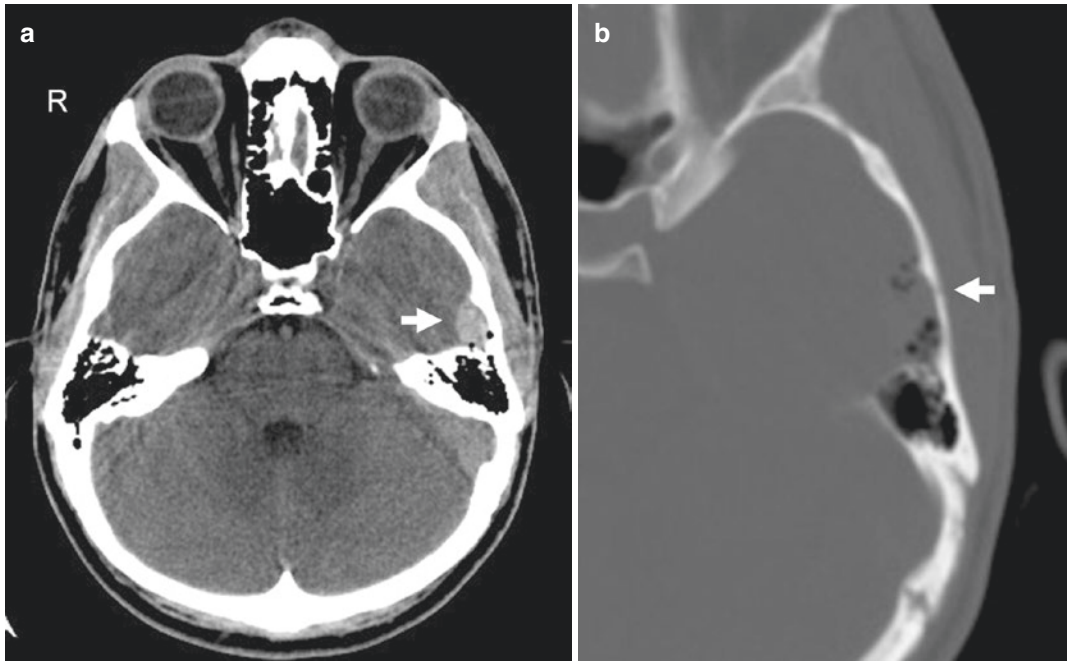

Fig. 6 Acute EDH. (**a**) Non-contrast axial CT shows a characteristic hyperdense, homogeneous, biconvex left temporal extra-axial collection (*arrow*). (**b**) An adjacent axial CT slice, displayed in bone window, reveals associated pneumocephalus and a linear non-displaced fracture of the left temporal bone (*arrow*)

region, where the fracture disrupts the partially embedded middle meningeal artery [113, 114]. EDHs are less common in young children because the pediatric skull is more compliant, and the meningeal groove is shallower. In children, EDHs may occur from stretching or tearing of meningeal arteries without an associated fracture. EDHs are also less common in the elderly because the dura in the elderly is more adherent to the inner table of the skull and is, therefore, not easily displaced.

On CT, an acute EDH appears as a well-defined biconvex hyperdense collection, with attenuation between 50 and 70 HU (Fig. 6a, b). On MRI, a thin dark line is observed along the inner margin of the EDH (Fig. 7). This line represents the two layers of dura, the periosteal and meningeal dura, that together are displaced by the EDH. Identification of this line confirms the epidural location of the hematoma, and this is very helpful in differentiating it from a subdural hematoma. Inward displacement of the venous sinuses away from the inner skull also serves as a clue that the hematoma is located within the epidural space. As is the case with hematomas

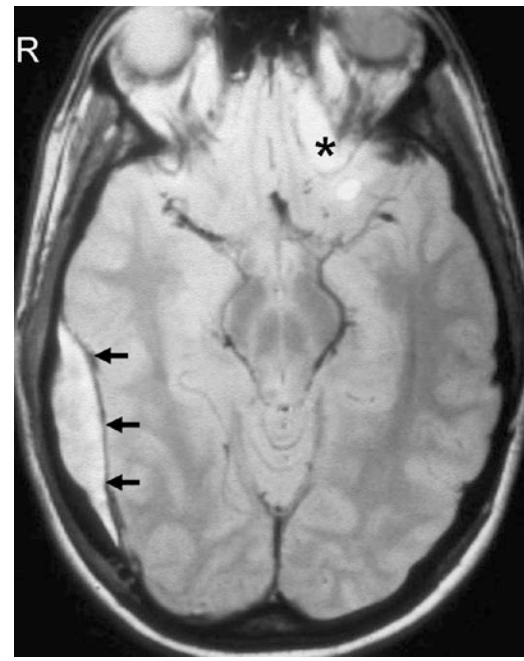

Fig. 7 Subacute EDH on MRI. Proton density-weighted axial MR image shows a thin dark line (*horizontal arrows*) displaced by the extra-axial collection, indicating the epidural location of the hematoma. A contrecoup left orbitofrontal contusion is also evident (*asterisk*). (Reprinted with permission of Wolters Kluwer from Gean [148])

elsewhere, the MR signal characteristics of the EDH correlate with the age of the blood products [115, 116].

It is important to scrutinize CT images of an EDH for the presence of a "swirl sign." A "swirl sign," recognized by the presence of low-density areas within the hyperdense hematoma, is thought to represent active bleeding (Fig. 8a, b) [117, 118]. Unclotted blood from active bleeding appears as low density and takes on the characteristic hyperdense appearance as it clots. The "swirl sign" forewarns of continued bleeding and rapid expansion of an arterial EDH. Patients with an expanding EDH tend to present early, with a lower GCS and a higher mortality rate [119]. Layering of clotted blood, denser than unclotted blood, may give rise to a "hematocrit sign" within an EDH. Signs of active bleeding can also be identified on a contrast CT. Contrast extravasation within low-density areas of an EDH has been reported to represent active hemorrhage from an underlying dural vessel laceration [120]. Thus, a "swirl sign" on non-contrast CT or active extravasation on contrast CT serves as radiological markers for EDH expansion and flag the need for urgent neurosurgical assessment.

Venous EDHs are less common than arterial EDHs, and they occur due to bleeding from meningeal and diploic veins or from the dural venous sinuses. The venous EDH is less frequently associated with a skull fracture than is the arterial EDH. Venous EDHs tend to occur in three classic locations: (1) the posterior fossa from rupture of the torcular herophili or transverse sinus (Fig. 9), (2) the anterior middle cranial fossa from disruption of the sphenoparietal sinus (Fig. 9a, b) [121, 122], and (3) at the cranial vertex due to injury to the superior sagittal sinus or cortical veins [107]. Unlike the arterial EDH, the venous EDH rarely expands beyond its initial size because of the lower pressure imposed by venous extravasation.

Subdural Hematoma

The *subdural hematoma* (SDH) occurs above the arachnoid and beneath the inner meningeal layer of the dura (Fig. 5). SDHs are intradural lesions, and, therefore, they do not respect the calvarial suture margins, as do their EDH counterparts.

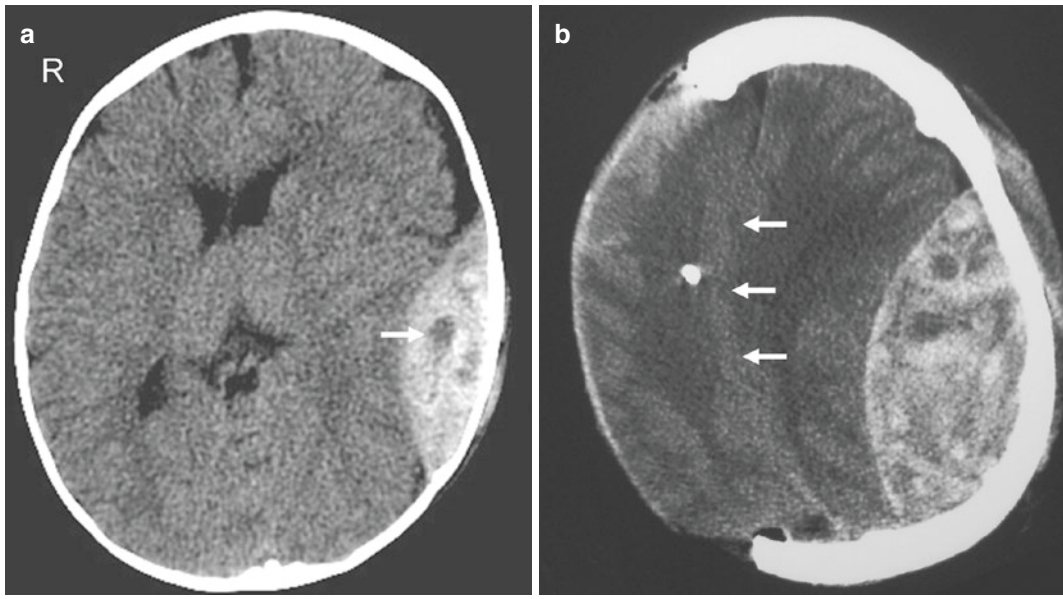

Fig. 8 EDH "swirl sign." (**a**) Axial CT image shows low attenuation areas (*arrow*) within a left frontotemporal heterogeneous acute EDH. The heterogeneous density within this EDH is secondary to mixing of hyperacute (low attenuation) with acute (high attenuation) blood. (**b**) Axial CT image from another patient, performed following decompressive craniectomy, demonstrates right external herniation, left-to-right subfalcine herniation (*arrows*), and formation of a contralateral, heterogeneous EDH

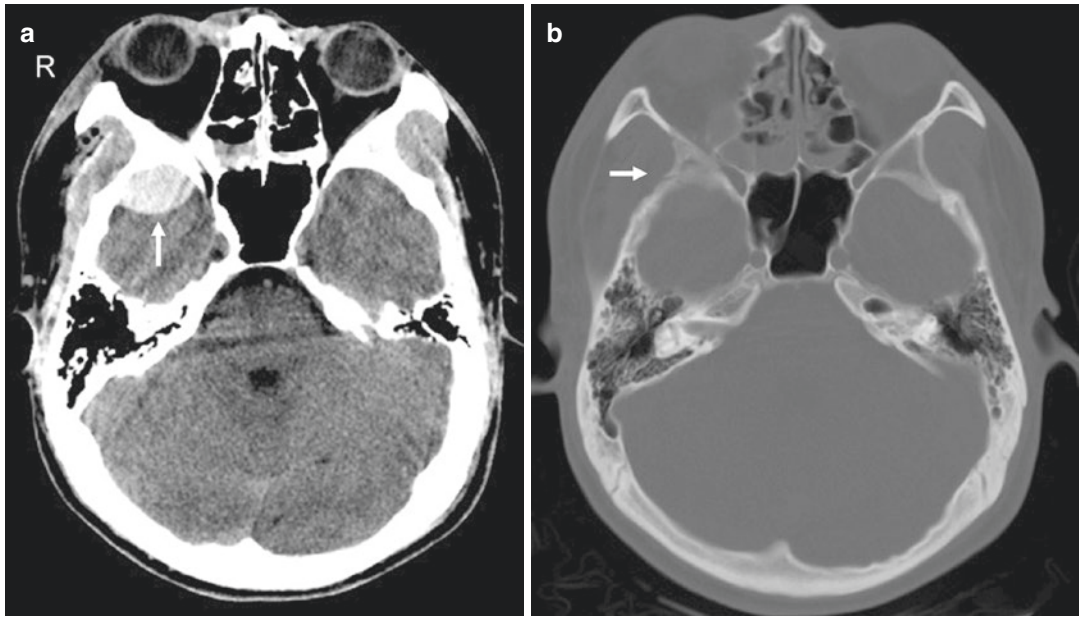

Fig. 9 Venous EDH. (**a**) Axial CT image shows a biconvex, homogeneous, high attenuation extra-axial collection within the right middle cranial fossa (*vertical arrow*). (**b**) CT image displayed in "bone window" reveals a fracture of the right greater sphenoid wing (*horizontal arrow*). The location suggests that the hematoma is due to disruption of the sphenoparietal sinus. (Both: Reprinted with permission of John Wiley and Sons from Le and Gean [121])

Most SDHs are supratentorial and located over the convexity, especially the parietal region. Because the dura and arachnoid are not firmly attached, the SDH is frequently seen layering over the entire hemispheric convexity from the anterior falx to the posterior falx. In trauma, collections of subdural blood are also frequently seen along the falx and the tentorium. Unlike EDHs, SDHs are predisposed to occur at the contrecoup site. The SDH may develop from laceration or disruption of bridging cortical veins. This is especially true during falls with sudden head deceleration in the elderly. Compared to younger patients, cerebral atrophy in the elderly places the bridging cortical veins at risk for stretch injury and allows for increased motion of the brain parenchyma within the calvarium. SDHs can also arise from injury to pial vessels, Pacchionian granulations, or penetrating branches of superficial cerebral arteries. At surgery, the bleeding source that gave rise to the traumatic SDH may not be evident.

On CT, the acute SDH appears as a hyperdense, homogenous, and crescent-shaped collection (Fig. 10a). Compared to normal brain (20–30 HU), the density (attenuation) of an acute SDH (50–60 HU) is higher because of clot retraction. In trauma, mass effect on CT imaging can be used to differentiate simple and complex SDHs. In simple SDHs, the degree of midline shift is directly proportional to the size of the acute SDH. Complex SDHs are associated with parenchymal brain injury, and the degree of mass effect and midline shift is more severe than the SDH collection itself would predict. In a complex SDH, CT imaging may also show subarachnoid hemorrhage, contusion injury, brain swelling, and other signs of parenchymal injury. The density of an acute SDH will progressively decrease over time, as protein degradation occurs and the SDH liquefies. Rebleeding during evolution of a SDH appears as a heterogeneous mixture of fresh hyperdense, acute blood and older, less dense, partially liquefied hematoma (Fig. 10b). A sediment level or "hematocrit effect" may be seen from either rebleeding or in patients with clotting disorders.

As the SDH undergoes hemolysis, its appearance on CT transitions from a hyperintense white

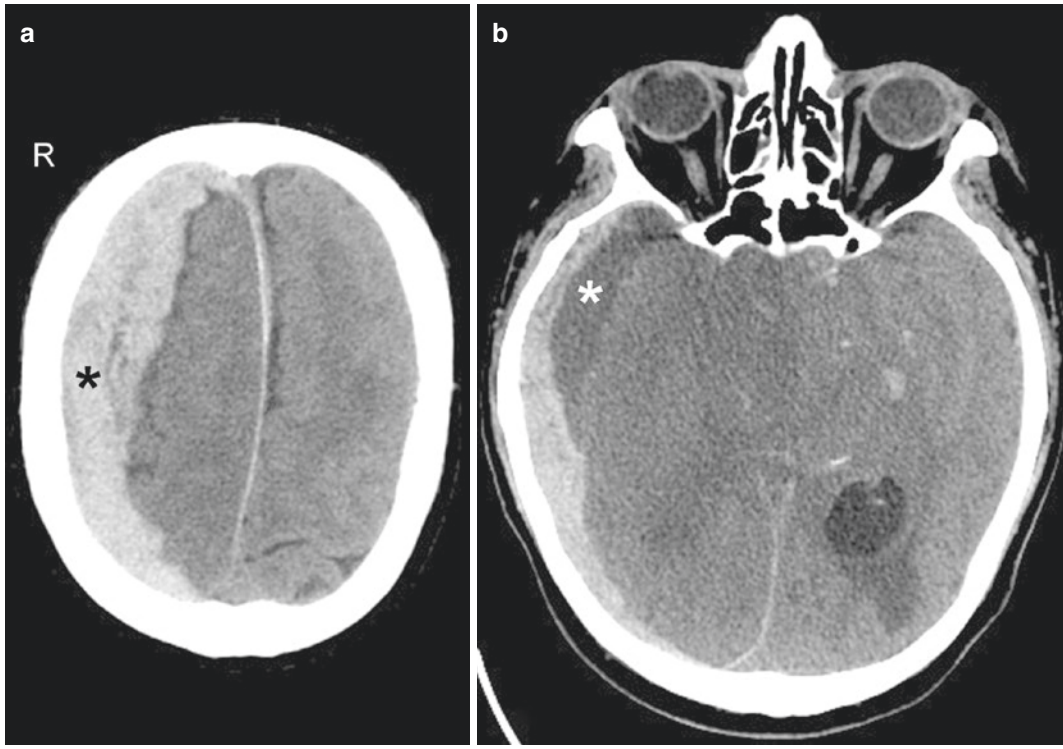

Fig. 10 SDH. (**a**) Non-contrast axial CT image demonstrates a right hyperdense, holohemispheric extra-axial collection (*asterisk*), causing mass effect and sulcal effacement of the right cerebral hemisphere. There is also mild right-to-left subfalcine herniation. (**b**) Non-contrast axial CT image shows a low-density area (*asterisk*) corresponding to a chronic SDH component within an acute right temporal SDH. There is associated loss of gray-white matter differentiation and diffuse decrease in attenuation of the right temporal lobe and midbrain due to cerebral edema and ischemia. There is effacement of the cisterns. Multiple foci of small hemorrhages within the left temporal lobe indicate axonal injuries. There is also dilatation of the occipital horn of the left ventricle

to hypodense dark gray collection. Between 1 and 3 weeks following injury, an isodense SDH phase occurs, wherein the Hounsfield characteristics of the SDH approximate those of the brain parenchyma. The timing depends on the patient's hematocrit level, clotting capability, and presence or absence of rebleeding. During this subacute period, an isodense SDH can be difficult to identify on CT (Fig. 11). Imaging findings, such as flattening of the cortical gyri, sulcal effacement, effacement or distortion of the white matter (white matter "buckling"), abnormal separation of the gray-white matter junction from the inner table of the skull ("thick gray matter mantle"), distortion of the ventricles, and midline shift are indirect signs that herald detection of an isodense SDH. Isodense SDHs are readily revealed on contrast CT imaging.

On CT, the chronic SDH has density similar to, but slightly higher than, cerebrospinal fluid (Fig. 12). It may be difficult to distinguish a small chronic SDH from prominent subarachnoid space in patients with cerebral atrophy. In these patients, a contrast-enhanced CT can improve detection of the chronic SDH by demonstrating an enhancing capsule or displaced cortical veins. Over time, activated fibroblasts and blood vessels from the dura organize within the chronic SDH. These newly formed vessels are fragile and are prone to bleeding, which can lead to the dreaded "chronic recurrent" SDH. The chronic recurrent SDH may not be crescentic in shape because of dural adhesions, and it is typically heterogeneous, with multiple internal septations, loculations, and fluid levels (Fig. 13f).

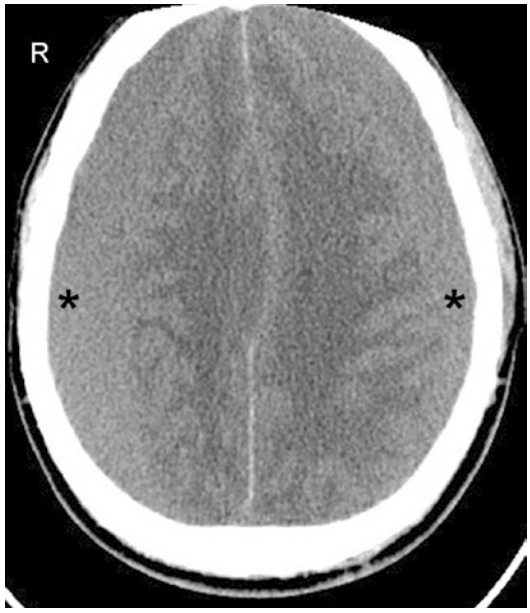

Fig. 11 Isodense subacute SDH. Non-contrast axial CT image shows bilateral isodense SDHs. During the transition from acute to chronic SDH, an isodense phase occurs. At this stage, the SDH (*asterisk*) can be difficult to differentiate from the adjacent brain parenchyma. Note displacement of the gray-white matter junction from the inner table of the skull (the "thick gray matter mantle" sign)

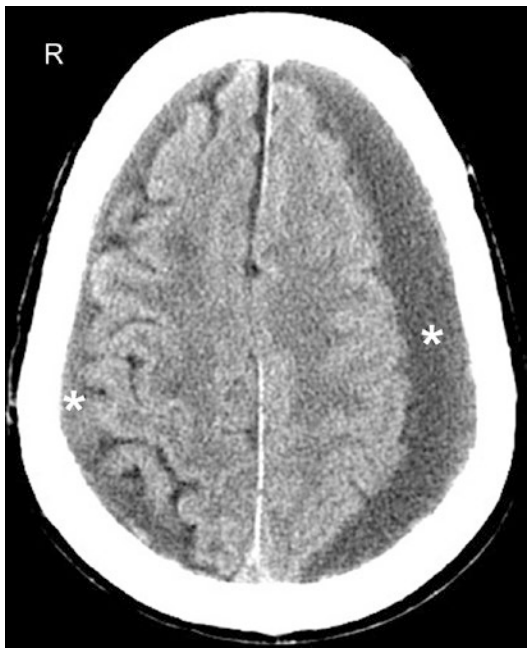

Fig. 12 Chronic SDH. Non-contrast axial CT image demonstrates bilateral low-density collections (*asterisk*) due to chronic SDHs. The chronic SDH has attenuation slightly higher than CSF

The MRI signal characteristics of the SDH vary depending on the age of the blood products [115, 116]. This renders MRI extremely useful for gauging the age of the SDH and dating the time of injury. The acute SDH is isointense to brain on T1-weighted images and hypointense on T2-weighted images. During the subacute phase, when the SDH is isodense on non-contrast CT images, the SDH has high signal intensity on T1-weighted images due to the presence of methemoglobin (Fig. 13a). Relative to normal brain, the chronic SDH appears hypointense on T1-weighted and hyperintense on T2-weighted images. The signal intensity of the chronic SDH is typically slightly higher than CSF signal intensity on T1- and T2-weighted and FLAIR images (Fig. 13b). The lack of beam-hardening artifact and the capability of multi-planar imaging make MRI particularly useful in identifying small convexity and vertex SDHs that may not be readily recognized on axial CT.

Subarachnoid Hemorrhage

Common sites for traumatic *subarachnoid hemorrhage* (SAH) include the Sylvian fissure, the interpeduncular cistern, and the high convexity. The greatest accumulation of SAH tends to occur on the contrecoup side. Traumatic SAH can occur as an isolated finding or in conjunction with other manifestations of brain injury. As an isolated finding, traumatic SAH is typically seen in mTBI patients. The SAH develops from disruption of small pial vessels due to the motion of the brain relative to the skull during the trauma. Traumatic SAH also accompanies displaced skull fractures, which injure the pial vessels. Contusions and traumatic hematomas with contiguous extension into the subarachnoid space and intraventricular hemorrhage with spread of blood into the SAH space via the fourth ventricular outlet foramina are sources of SAH that accompany moderate and severe TBI injuries.

Traumatic SAH may also accompany vascular dissection injuries. SAH concentrated in the foramen magnum, medullary, and prepontine cisterns of the posterior fossa, with a paucity of SAH or other signs of trauma in the supratentorial compartment, should raise suspicion for a vertebral

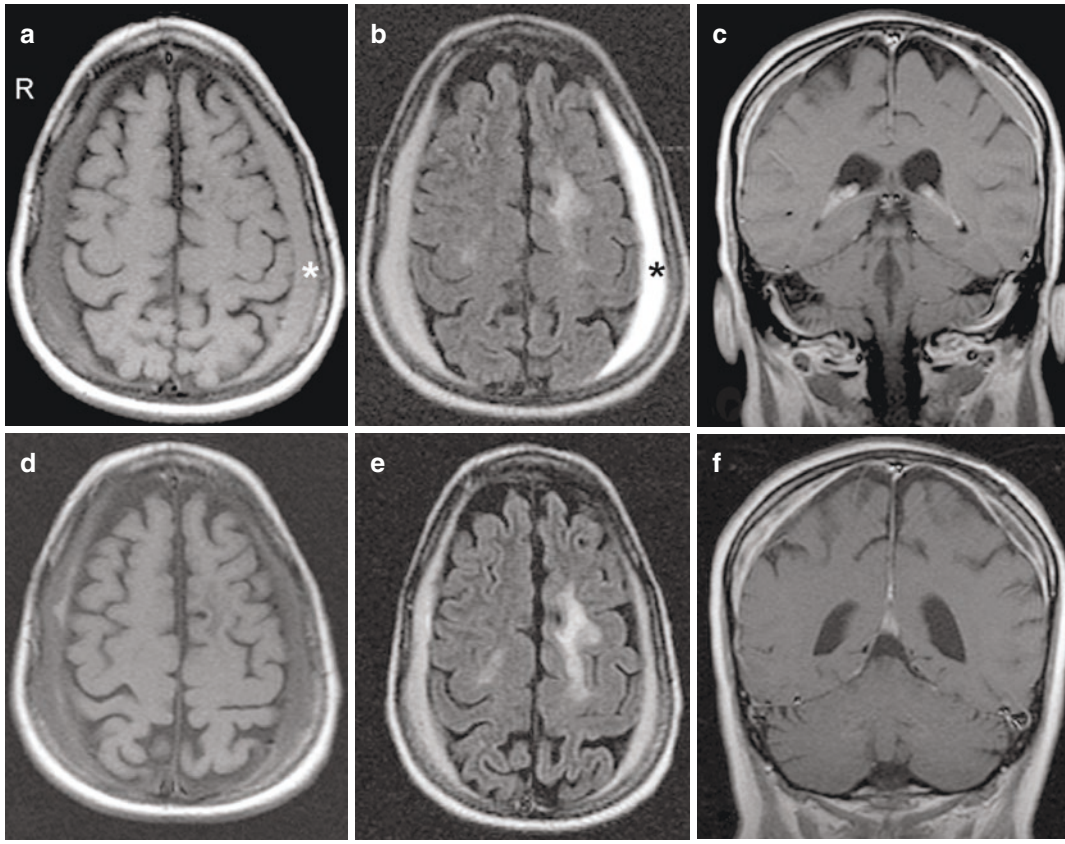

Fig. 13 MRI of SDH. (**a**) Axial T1-weighted MR image, performed on a 0.7 T open MRI, reveals bilateral holohemispheric SDHs. The subacute left SDH has signal intensity relatively higher than adjacent parenchyma due to the presence of methemoglobin. (**b**) The corresponding FLAIR image shows that the subacute left SDH is quite intense. The chronic right SDH has signal intensity higher than the suppressed CSF signal. (**c**) The SDHs also have enhancing capsules, as seen on the coronal T1-weighted post-contrast image. (**d**) Axial T1-weighted image, performed 2 months later, shows evolution of the left SDH, which is now low in intensity. (**e**) Both SDHs are now of similar intensity on FLAIR. (**f**) Coronal T1-weighted post-contrast image shows heterogeneous enhancement within the right SDH due to the presence of activated fibroblasts and blood vessels from the dura organized within the SDH

artery dissection. Vertebral artery injury may occur without signs of posterior fossa trauma, and CT imaging of the cervical spine may be unremarkable. Even though the burden of SAH is often significant, these injuries are easily overlooked. The presence of intracranial SAH within the well-protected bony confines of the posterior fossa belies the vascular injury.

In the setting of trauma, the assessment of SAH in the Sylvian fissure can be challenging. It can be very difficult to differentiate spontaneous SAH due to aneurysmal rupture from traumatic SAH. Additional findings of parenchymal injury juxtaposed to the Sylvian fissure tend to support a traumatic etiology. Localization of SAH to the contrecoup Sylvian fissure also favors a traumatic etiology. Additional complexity derives from the possibility that the trauma is secondary to spontaneous rupture of an underlying middle cerebral artery aneurysm and that the imaging findings are a composite of these two events. Equipoise regarding the etiology of Sylvian fissure SAH should be an indication for further investigation, typically with a CTA or MRA study.

On CT, acute SAH appears as areas of high density that conform to the morphology of the

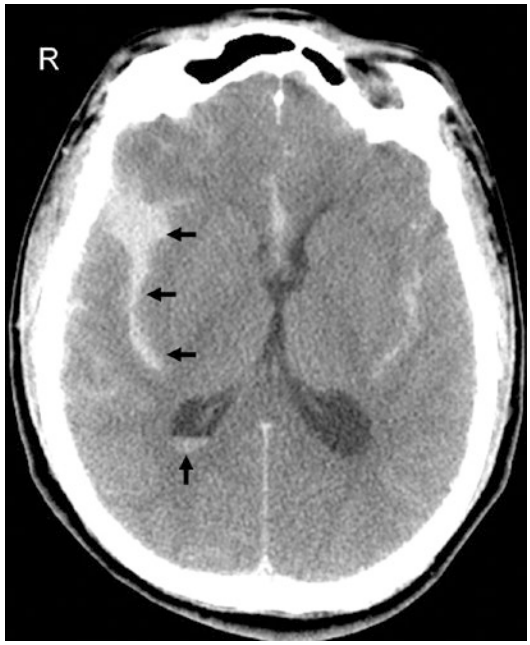

Fig. 14 SAH and IVH. Non-contrast axial CT image demonstrates bilateral high attenuation collections conforming to the Sylvian sulcus due to acute SAH. The greatest collection of SAH is within the right Sylvian sulcus (*horizontal arrows*). Small high-density collection layering within the occipital horn of the right lateral ventricle is compatible with acute IVH (*vertical arrow*)

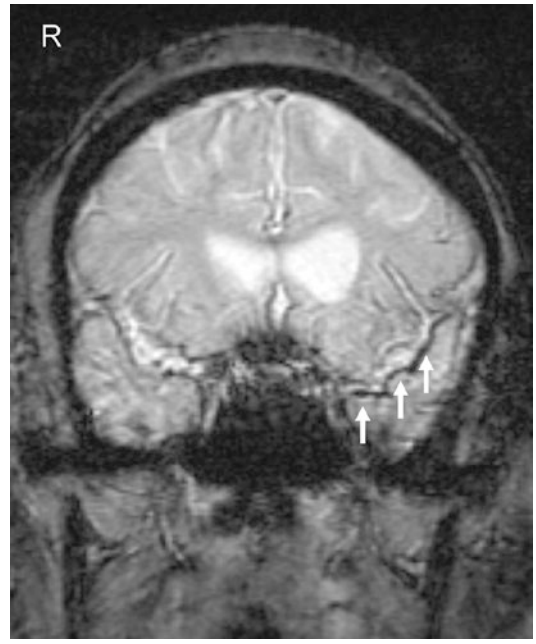

Fig. 15 Chronic SAH on GRE MRI. Coronal GRE T2∗-weighted image demonstrates bilateral decrease in signal within the temporal sulci, with the greatest accumulation within the left Sylvian sulcus (*arrow*) due to hemosiderin deposits (superficial siderosis)

cerebral sulci and cisterns (Fig. 14). SAH along the convexity or tentorium can be difficult to differentiate from a SDH. A useful distinguishing clue is the extension of the SAH into adjacent sulci. Occasionally, "effacement" of the sulci due to the presence of intra-sulcal SAH is the only imaging finding to alert one to the presence of SAH. False-positive diagnosis of SAH can arise from failure to recognize that two adjacent gyri compressed against each other can accentuate their pial markings, mimicking SAH. This can occur, for example, in the setting of diffuse cerebral swelling with intrinsic mass effect within cerebral gyri.

Acute SAH is more difficult to detect on conventional T1- and T2-weighted MRI than on CT. This is because the constituents of acute blood, intracellular oxyhemoglobin and/or deoxyhemoglobin, are isointense to brain parenchyma and are difficult to detect when thinly dispersed in SAH. However, FLAIR is potentially more sensitive than CT for detection of acute SAH, especially when the volume of SAH measures at least 1–2 mL [47]. In intubated patients on high concentrations of inspired oxygen, the weakly paramagnetic properties of oxygen can cause FLAIR sequences to give a false-positive diagnosis of SAH [50]. Subacute SAH, when the blood is isointense to CSF on CT, is better recognized on MRI because of the high signal intensity of extracellular methemoglobin at this stage. SAH more than 1-week old would be difficult, if not impossible, to detect on CT. Chronic SAH is better detected on MRI and is invisible on CT. Old blood products, such as hemosiderin in the subarachnoid space ("superficial hemosiderosis"), are best detected on SWI and GRE T2∗-weighted images (Fig. 15) and appear as areas of decreased signal intensity.

Intraventricular Hemorrhage

Traumatic *intraventricular hemorrhage* (IVH) can result from rotationally induced tearing of subependymal veins along the surface of the ven-

tricles or from contiguous extension of blood from a parenchymal contusion or hematoma into the ventricular system (Fig. 14). Direct penetrating wounds can also cause IVH. Patients with IVH are at risk for developing non-communicating hydrocephalus from obstruction of the aqueduct due to ependymal proliferation ("ependymitis") and/or communicating hydrocephalus from obstructive scarring of the arachnoid villi.

On CT, acute IVH typically appears as a hyperdense collection layering dependently within the ventricular system and forming a CSF-blood fluid level (Fig. 14). Sometimes, a tiny collection of increased density layering posteriorly in one occipital horn may be the only clue to IVH. Occasionally, the IVH appears "tumefactive" or "mass-like" as a cast within the ventricle.

Primary Intra-axial Injury

Traumatic Axonal Injury

Traumatic axonal injury (TAI) (previously termed diffuse axonal injury or DAI) refers to white matter damage arising from shear-strain deformation of brain tissue following rotational acceleration and deceleration injury. When the skull is rapidly rotated, axial stretching, separation, and disruption of the white matter fibers occur as the brain and skull move at different speeds relative to one another. TAI entails injury to the axons in the white matter and occurs in up to 50% of severe head trauma injuries [123]. TAI lesions may associate with microhemorrhage. TAI is of special interest, because it is believed to be a mechanism to account for unexplained cognitive deficits following head trauma. TAI is underdiagnosed by conventional imaging techniques [124, 125].

TAI has a predilection for three classic regions ("shearing injury triad"): the lobar white matter, the corpus callosum, and the dorsolateral quadrant of the rostral brainstem adjacent to the superior cerebellar peduncle. The location of TAI generally correlates with the severity of the trauma [126]. Mild (Grade I) TAI typically involves only the peripheral gray-white junction of the lobar white matter, commonly the parasagittal regions of the frontal lobes and the temporal stem (Fig. 16a–d). With moderate (Grade II) TAI, the corpus callosum, particularly the posterior body and splenium, in addition to the lobar white matter, is involved (Fig. 17a, b). In severe (Grade III) TAI, the dorsolateral midbrain, in addition to the lobar white matter and corpus callosum, is affected.

On CT, TAI lesions are detected as small high attenuation foci (shear hemorrhages) at the gray-white junction of the cerebral hemispheres (Fig. 16), corpus callosum, and the dorsolateral midbrain, depending on the severity of the trauma. The sensitivity of CT to detect TAI is dependent on the burden of microhemorrhage that accompanies the shear injury. Because of its higher sensitivity to blood products, GRE T2∗-weighted MRI reveals more hemorrhagic TAI lesions than CT [125]. Even so, detection of hemorrhagic shear alone does not fully describe the extent of TAI [127]. FLAIR sequences can identify nonhemorrhagic foci of TAI, but FLAIR MRI still underestimates the true extent of the diffuse white matter damage [48]. Nonhemorrhagic acute TAI lesions appear as multiple small foci of increased signal on T2-weighted images and decreased signal on T1-weighted images. On DWI, acute TAI can show reduced ADC (Fig. 18d) and reduced FA. In subacute TAI, intracellular methemoglobin from microhemorrhage appears as an area of central hypointensity on T2-weighted images and hyperintensity on T1-weighted images. Over time, the conspicuity of TAI on MRI eventually diminishes as the damaged axons degenerate, the edema resolves, and the microhemorrhage resorbs. Chronic TAI imaging findings include nonspecific atrophy, gliosis, Wallerian degeneration, and hemosiderin staining. Focal areas of reduced FA may be detected in chronic TAI.

MRI is superior to CT in detecting axonal injuries, especially when susceptibility-weighted sequences and higher field strength magnets (3T) are used [128]. Even then, the ability of conventional MRI imaging to detect TAI lesions is inadequate. Advanced MR imaging methods, such as SWI and DTI with 3D tractography (Fig. 18), provide additional modalities for the detection of white matter injury in both acute and chronic TAI.

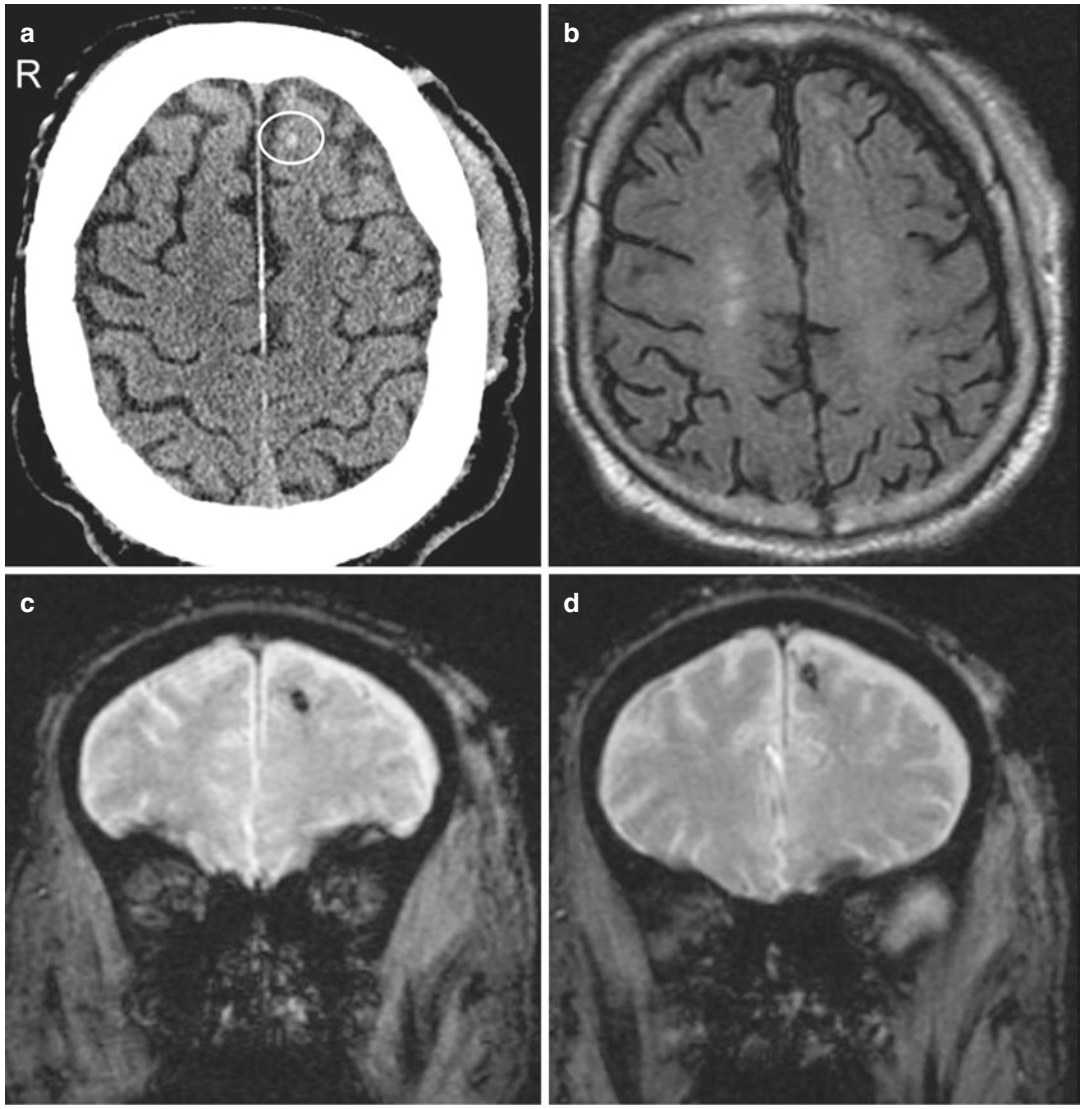

Fig. 16 Grade I TAI. (**a**) Non-contrast axial CT image reveals a small high-density focus within the subcortical white matter of the left frontal lobe, compatible with hemorrhagic shear injury. (**b**) Follow-up axial FLAIR image demonstrates a corroborated subcortical focus of T2 hyperintensity. There is an additional left frontal subcortical focus of FLAIR hyperintensity that is not visible on the CT image. Nonspecific T2 signal abnormality within the bilateral centrum semiovale is also noted. (**c, d**) Coronal GRE T2∗-weighted images show corresponding foci of hemorrhagic shear injury within the left frontal lobe

Cortical Contusion

The *cortical contusion* is a hemorrhagic parenchymal injury ("brain bruise") involving predominantly the superficial gray matter with relative sparing of the underlying white matter. Areas of brain that are in close contact with the rough inner surfaces of the skull are predisposed to contusion injury. Regions within the temporal lobes (above the petrous bone and posterior to the greater sphenoid wing) and the frontal lobes (above the cribriform plate, orbital roof, and lesser sphenoid wing) are commons sites for contusions. Contusions occur as both coup and contrecoup injuries. Depressed skull fractures often keep company with subjacent contusion injury. Contusions along the parasagittal convexity are

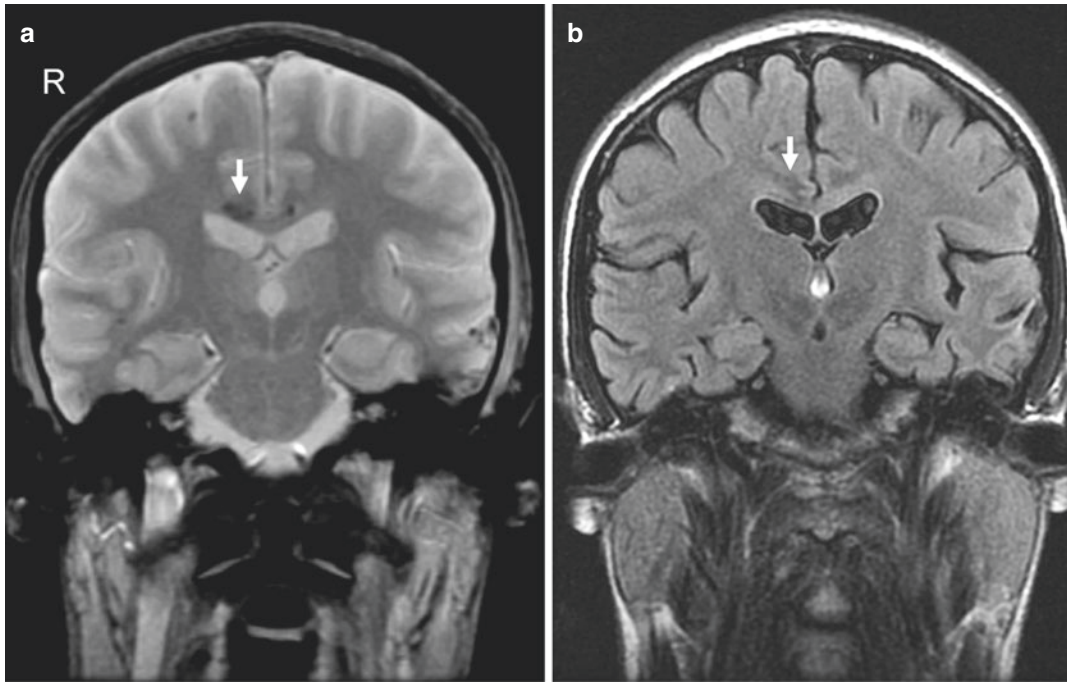

Fig. 17 Grade II TAI. (**a**) Coronal GRE T2∗-weighted image demonstrates multiple foci of low signal (hemorrhages) within the peripheral gray-white junction of the bilateral temporal and right frontal lobes. Abnormal foci of low signal are also seen within the corpus callosum (*arrow*). (**b**) The callosal injury is low in signal intensity on FLAIR (*arrow*) and is not as easily detectable

less common, and the cerebellum is infrequently involved [129].

On CT, hemorrhagic contusions appear as mottled areas of high density within the superficial gray matter (Fig. 19a). Contusion injuries incite vasogenic edema. Within hours of injury, contusions become surrounded by large areas of low density, corresponding to the associated brain edema. As the contusion evolves, a "salt and pepper" pattern of mixed areas of hypodensity and hyperdensity is characteristic. Due to its superficial location, a small cortical contusion can be masked on CT by beam-hardening streak artifacts from the skull.

Serial imaging of contusion lesions can reveal interim change with severalfold increases in the size of a contusion [130]. In the evolution of contusions, coalescence of disparate sprinklings of petechial hemorrhage can lead to contiguous patches of bleeding or even frank traumatic intracerebral hematomas. Contusion blossoming is a term applied to the dramatic expansion of contusion lesions. Initial small, focal contusions without mass effect can evolve into large lesions with local mass effect, midline shift, ventricular effacement, and compression of the basal cisterns. On a contrast CT performed within 6 hours of injury, contrast extravasation in contused areas of injury significantly associates with findings of contusion blossoming, hemorrhagic progression, and contusion edema at 24 and 72 hours [131].

MRI can provide better delineation of contusions than CT, since the skull does not distort the MR images of the brain parenchyma. On both T1- and T2-weighted MRI images, contusions appear as ill-defined areas of variable signal intensity, depending on the age of the lesions. Since contusions mainly involve cortex near the surface of the brain, they may have a "gyral" morphology. An old contusion commonly evolves into a wedge-shaped area of peripheral encephalomalacia with its broad base facing the skull. In this way, it can mimic an old ischemic infarction.

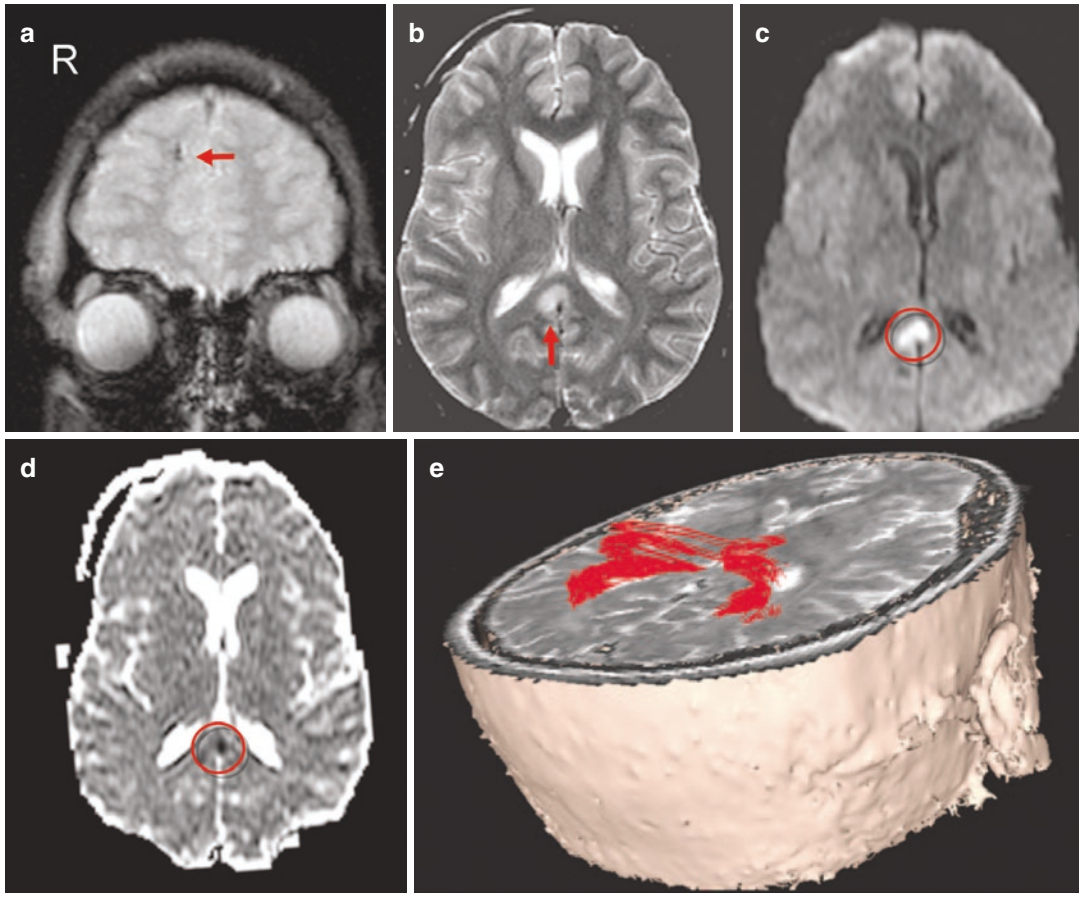

Fig. 18 Grade II TAI (acute) on DWI. (**a**) Coronal GRE T2∗-weighted MR image reveals a focus of dark signal (*arrow*) at the gray-white junction of the right frontal lobe consistent with hemorrhagic shearing injury. (**b**) T2-weighted image shows abnormal bright signal within the splenium (*arrow*) of the corpus callosum. Diffusion-weighted image (**c**) and corresponding ADC map (**d**) show restricted diffusion in the same area (*circle*). (**e**) 3D color tractography demonstrates disruption of the commissural fibers at the posterior inferior margin of the splenium of the corpus callosum. (Both: Reprinted with permission of Oxford University Press from Le et al. [58])

Intracerebral Hematoma

The *intracerebral hematoma* (ICH) can develop at the time of impact from microcavitation or shear-induced hemorrhage of small intraparenchymal blood vessels. Traumatic ICH can also evolve from expansion and progression of a contusion injury. Coagulopathy can be an inciting factor in the progression of a contusion into an ICH. Contusions and traumatic ICH often coexist together. ICHs frequently involve the orbitofrontal and anteroinferior temporal white matter. Compared to contusions, traumatic ICHs are deeper, more extensive lesions and are often associated with a higher burden of additional TBI injuries. These features may signify an increased severity of the impact, as patients often present as severe TBI. Contusions and traumatic ICHs have characteristic differences on imaging. Compared to a cortical contusion, the traumatic ICH is usually more well-defined, tends to have less surrounding edema, and is located deeper with significant involvement of the white matter.

On CT, the acute intracerebral hematoma appears as a rounded hyperdense mass (Fig. 20a, b). As the hematoma evolves, a low-density rim, due to edema and pressure necrosis, can be observed. Contrast ring-enhancement can be seen within a subacute traumatic ICH because of the

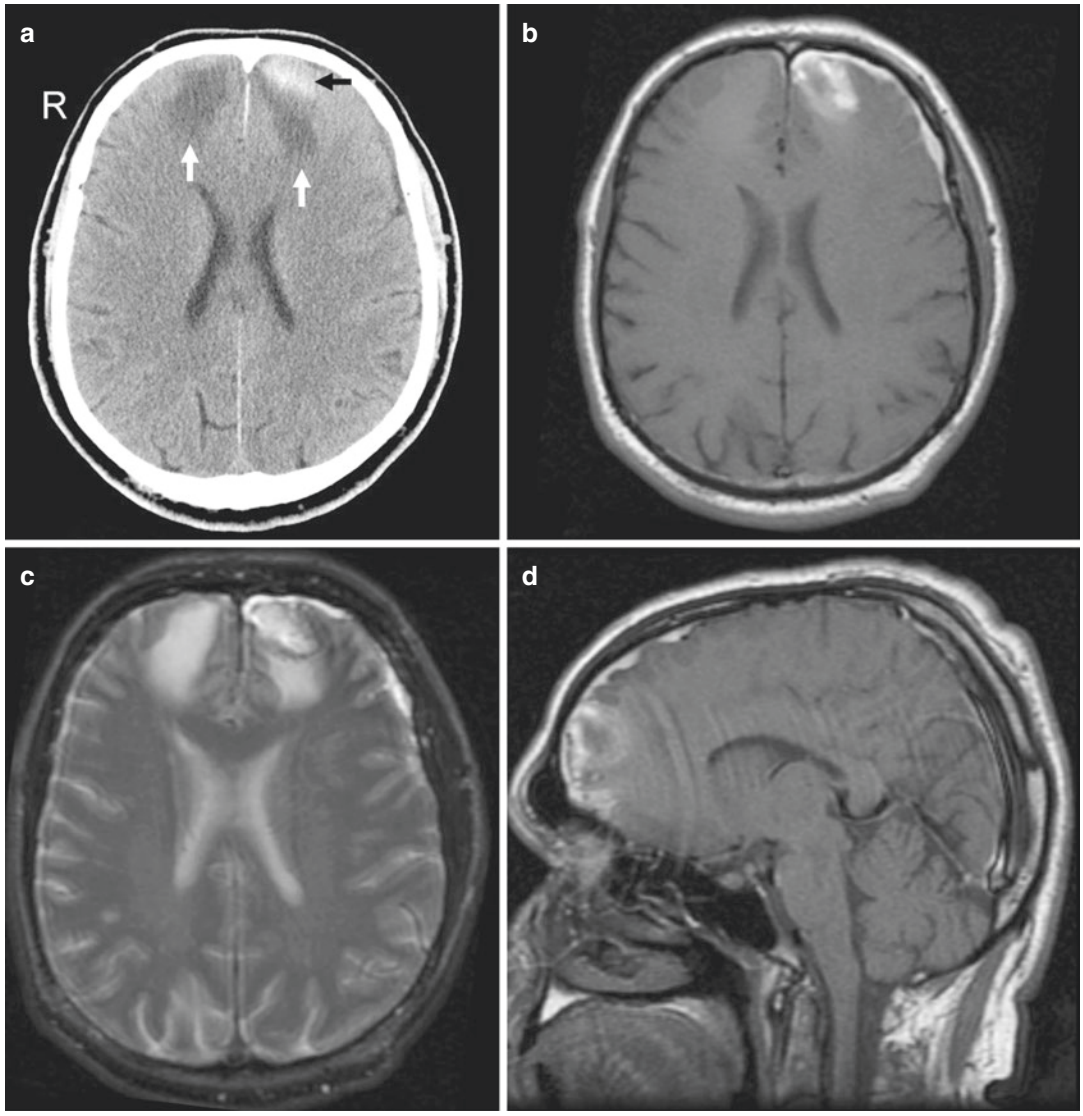

Fig. 19 Contusion on CT and MRI. (**a**) Axial CT shows an amorphous high-density area within the left orbitofrontal lobe consistent with an acute contusion (*horizontal arrow*). Bilateral frontal lobe low attenuation (*vertical arrow*) represents either vasogenic edema and/or nonhemorrhagic contusion. (**b**) Follow-up axial T1-weighted MR image shows corresponding high signal due to the presence of methemoglobin. A thin left SDH is also noted. (**c**) Axial T2-weighted image shows the left hemorrhagic contusion of mixed high and dark signal, while the bilateral frontal nonhemorrhagic contusions versus vasogenic edema are more homogenous in appearance. (**d**) Sagittal T1-weighted MR image displays an area of left inferior frontal surface contusion, in addition to the more superior contusion and the left SDH seen in (**b**)

proliferation of new capillaries lacking a complete blood-brain barrier. The enhancing subacute ICH can be difficult, if not impossible, to differentiate from an abscess, infarct, or neoplasm without accurate clinical history or novel imaging methods such as MRS or DWI. The imaging findings of the chronic intracerebral hematoma are nonspecific. Traumatic ICHs often develop in the process of contusion evolution and "contusion blossoming." The pathogenesis is not fully understood. Reperfusion hemorrhage secondary to vasospasm with subsequent vasodilation, break-

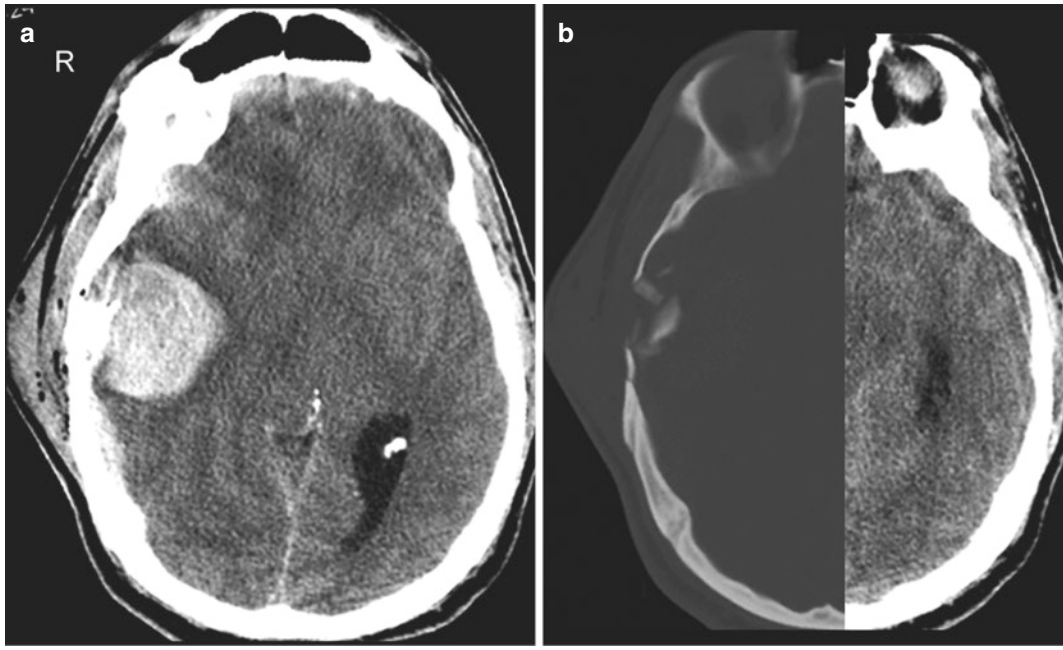

Fig. 20 ICH and skull fractures. (**a**) Non-contrast axial CT image from a patient who sustained a snowboarding accident shows a large, round, right posterior frontal intra-axial high attenuation mass due to an acute intracerebral hematoma. There is marked adjacent scalp soft tissue swelling. (**b**) CT image, displayed in bone window, reveals a comminuted depressed skull fracture

through bleeding arising from hypotension followed by hypertension, and underlying coagulopathy have been ascribed to account for this process. Dispersed small foci of contusion injury can simultaneously "blossom," leading to traumatic ICHs in multiple lobar locations, an event typically associated with a poor prognosis for the patient (Fig. 21a, b).

Encephalomalacia

Encephalomalacia is softening or loss of brain parenchyma, typically appearing following TBI as a focal well-defined area of tissue loss with compensatory dilatation of the ipsilateral ventricle and sulci. Old blood products and hemosiderin may be evident. Areas of encephalomalacia may incorporate one or more cyst cavities. Macrocystic encephalomalacia has the signal characteristics of CSF on both CT and MR. Microcystic encephalomalacia appears as low signal intensity on T1-weighted MR images and high intensity on T2-weighted and FLAIR images.

Vascular Injury

Traumatic injuries to the cerebral vasculature can result from blunt or penetrating trauma and include arterial dissections, pseudoaneurysms, and arteriovenous fistulae. Vascular injuries are often seen in association with skull base fractures. The internal carotid artery is the most commonly injured vessel. The injury usually occurs at sites of relative fixation, where the internal carotid artery enters the carotid canal at the base of the petrous bone and at its exit from the cavernous sinus beneath the anterior clinoid process.

Arterial Dissection

A traumatic *arterial dissection* develops when there is incomplete disruption of the vessel wall with formation of a subintimal or intramural hematoma. The dissection is often best detected with T1-weighted MR images with fat suppression where the hematoma appears as a bright "crescent sign" (Fig. 22). The affected vessel may appear irregular with relatively smaller cali-

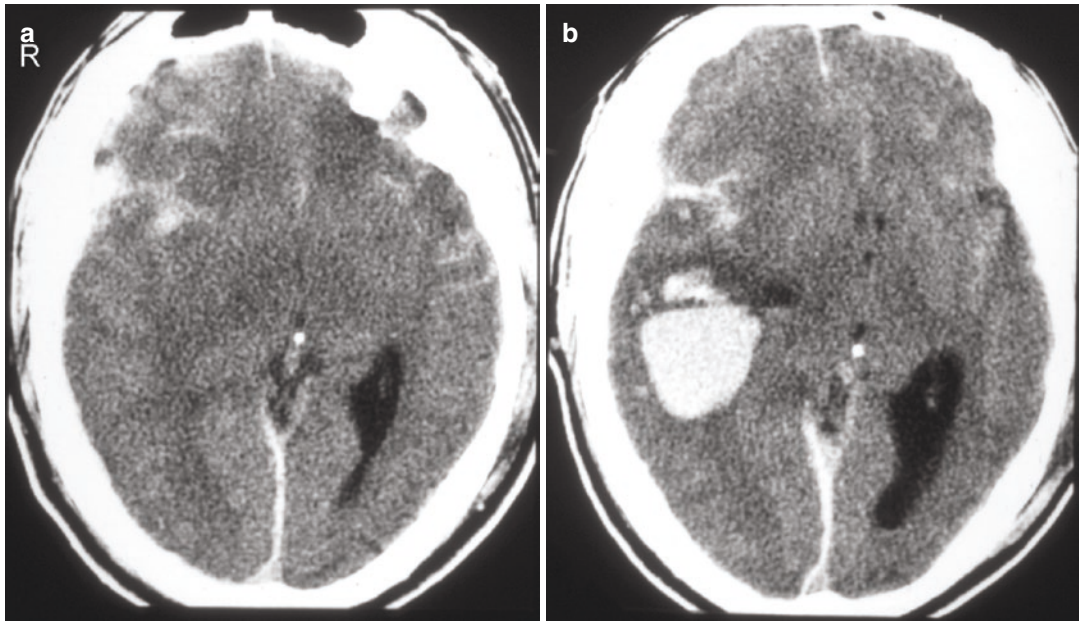

Fig. 21 "Delayed" intracerebral hematoma. (**a**) Noncontrast axial CT scan on admission demonstrates bilateral frontotemporal subarachnoid hemorrhages, right-to-left midline shift, and effacement of the right occipital horn, but without focal mass lesion. (**b**) The 4-hour follow-up study reveals interval development of a large right temporal hematoma in the area of prior mass effect. (Both: Reprinted with permission of Wolters Kluwer from Gean [151])

ber. Absence of the normal flow void, flow-related enhancement secondary to slow flow, intraluminal thrombus, or vessel occlusion may be identified on MRI and MRA. A watershed and/or embolic parenchymal infarction in the territory supplied by the injured vessel may be evident. Vessel wall imaging at 3T, as compared to 1.5 T, provides superior signal to noise ratios with significantly improved detection of intimal flaps and intramural hematomas [132]. MR techniques are being further developed to enable high-resolution imaging of pathological processes in cerebral vessel walls [133].

Conventional catheter angiography, traditionally, has been considered the gold standard for confirmation and delineation of a vascular dissection injury. Routinely, MRA and CTA are increasingly used as noninvasive tests to diagnose arterial dissections. Catheter angiography is useful for the workup of questionable findings on CTA or MRA. Compensatory collateral flow patterns in response to flow-limiting dissections can be tracked angiographically, enabling a detailed understanding of the hemodynamic impact and ischemic risk of the dissection. Angiography can also reveal associated vasospasm and pseudoaneurysm formation. Catheter angiography demonstrates the caliber of the patent lumen, while MRA and CTA are superior for detection of an intramural hematoma, subintimal flap, or other vessel wall injury which does not impede flow. Catheter angiography is often an adjunct to endovascular treatment of arterial dissections with stents or techniques of vessel sacrifice.

Pseudoaneurysm

A *pseudoaneurysm* often arises from a focal arterial dissection ("dissecting pseudoaneurysm") (Fig. 22b, c). All three layers of the vessel have been disrupted, and the wall of the pseudoaneurysm is actually an encapsulated hematoma in communication with the artery. Nevertheless, the wall of the pseudoaneurysm provides little support, and, hence, it has a propensity to hemorrhage. Pseudoaneurysms are rare in adults but account for 11% of all pediat-

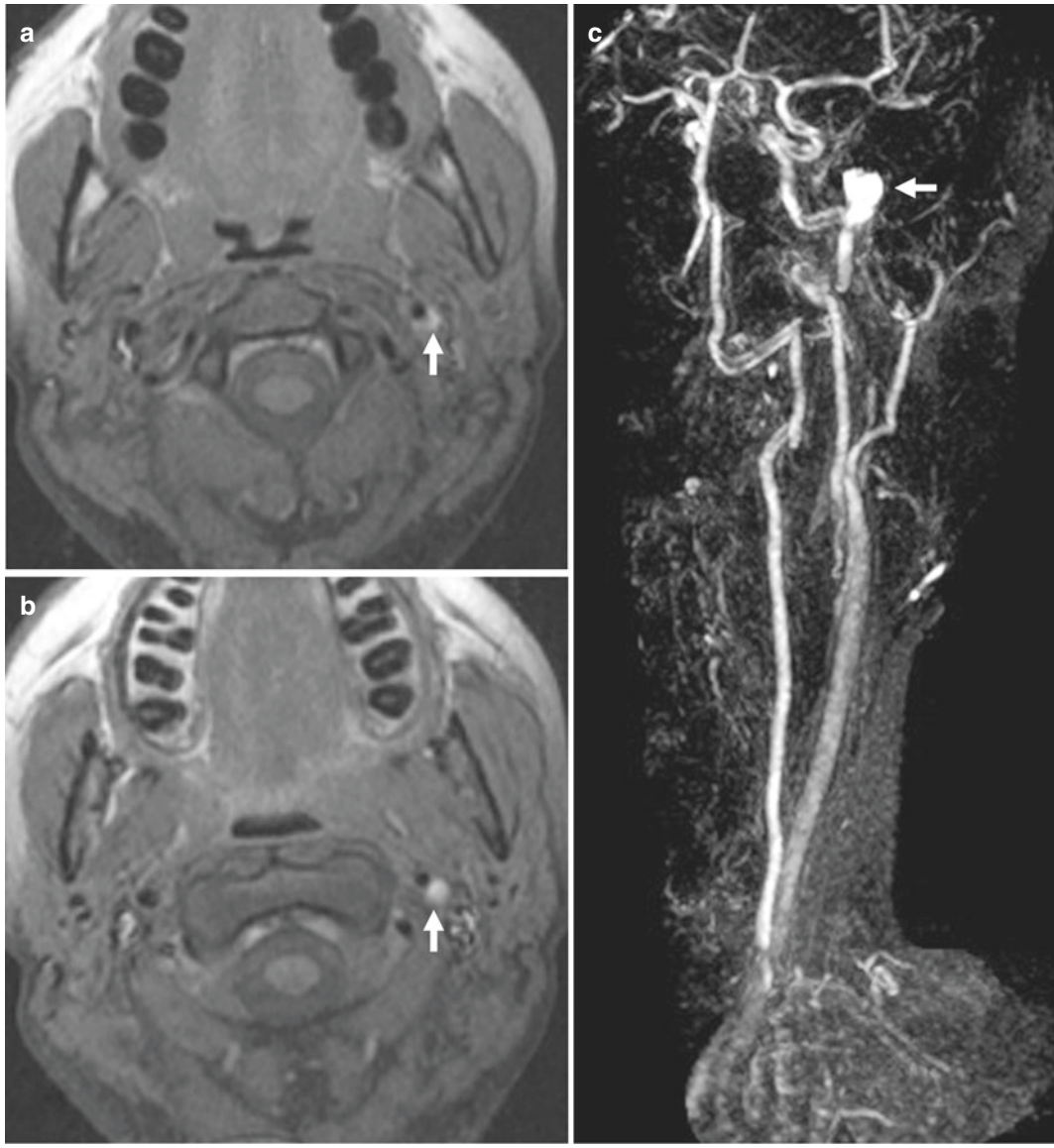

Fig. 22 Arterial dissection and pseudoaneurysm. (**a**) Axial T1-weighted with fat suppression image demonstrates a left common carotid artery high-intensity rim due to an intramural hematoma from a focal dissection (*arrow*). (**b**) Image superior to the focal dissection shows a round extra-luminal high-density focus (*arrow*). (**c**) MRA of the neck shows a lobular "mass" protruding from the vessel, compatible with a pseudoaneurysm (*arrow*)

ric aneurysms [134, 135]. In adults, traumatic pseudoaneurysms are common in the posterior fossa and are associated with significant morbidity and mortality [136]. Traumatic pseudoaneurysms of the posterior fossa are generally considered to evolve from a vertebral artery dissection injury. They most commonly occur at the junction of the posterior inferior cerebellar artery (PICA) and the vertebral artery. On early imaging studies following injury, the pseudoaneurysm may not yet have formed or it may be small and escape detection. Often unrecognized, pseudoaneurysms of the posterior fossa have high risk for catastrophic aneurysmal rupture, usually within the first 1–2 weeks following the initial trauma. Some recommend that patients

with traumatic vertebral dissections be screened, within the first 2 weeks after an initial injury, for interval development of a pseudoaneurysm [136]. CTA has been reported to be more sensitive than MRA for the detection of vertebral artery pseudoaneurysms [137]. On imaging, the pseudoaneurysm frequently has an irregular contour and a wide neck. Thrombosis may be present within large pseudoaneurysms and manifest as concentric laminated rings of heterogeneous signal intensity, consistent with thrombus in various stages of evolution (Fig. 23a). The size of a partially thrombosed pseudoaneurysm is underestimated on conventional angiography because the angiogram only depicts the patent portion of the lesion. MRI and CT can better reveal the true extent of a partially thrombosed pseudoaneurysm than angiography. In the absence of thrombosis or turbulent flow, the pseudoaneurysm appears as a round area of signal void on both T1- and T2-weighted MRI. Pulsation within a pseudoaneurysm may show phase artifacts on MRI, a helpful imaging clue to the presence of a vascular lesion.

Arteriovenous Fistula

The traumatic *arteriovenous fistula* (AVF) is a direct communication between an artery and a vein. Traumatic AVFs are uncommon injuries and can occur following either blunt or penetrating TBI. In blunt TBI, traumatic AVFs generally arise from vascular injury associated with skull base fractures. Anatomically, an artery and vein closely juxtaposed to one another is required to enable an AVF to form. The *carotid cavernous fistula* (CCF) involves a direct communication between the cavernous portion of the internal carotid artery and the adjacent cavernous sinus venous plexus (Fig. 24a–c). Direct CCFs typically result from a full-thickness injury to the cavernous segment of the internal carotid artery. They may also arise from rupture of a traumatic pseudoaneurysm of the cavernous internal carotid artery. Fracture of the sella turcica is commonly the source of injury to the cavernous carotid artery in a traumatic CCF. Skull base fractures, especially those involving the sphenoid bone, should prompt a search for signs of an associated cavernous carotid injury. Dilation of one or both superior ophthalmic veins

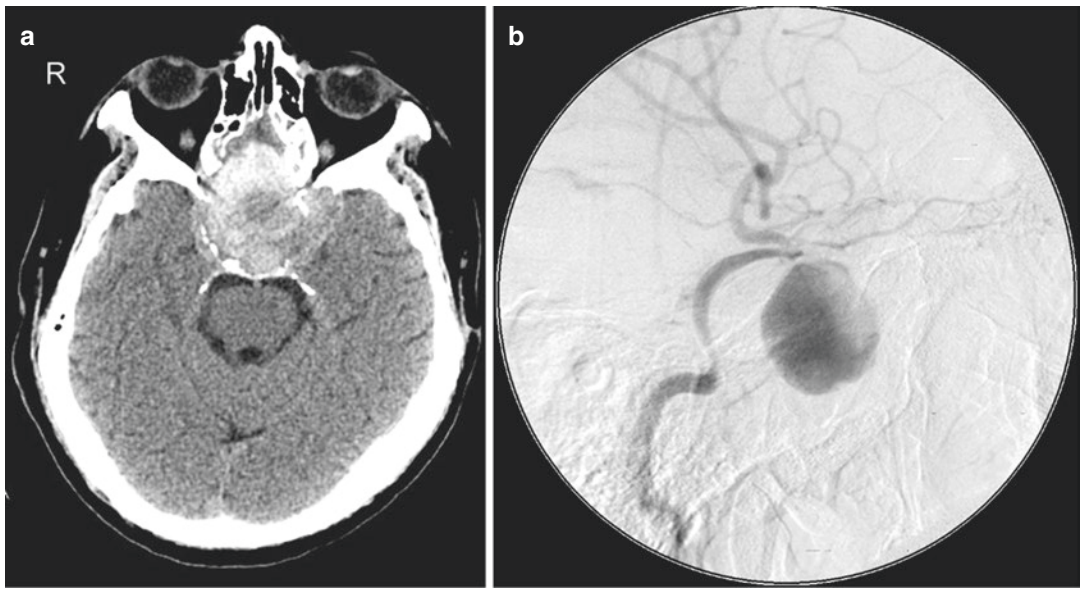

Fig. 23 Giant pseudoaneurysm. (**a**) Non-contrast axial CT image shows a large mixed low and high attenuation suprasellar mass. (**b**) Corresponding catheter cerebral angiogram from a selective left ICA injection shows a large mass partially filled with contrast arising from the left ICA, compatible with a partially thrombosed pseudoaneurysm

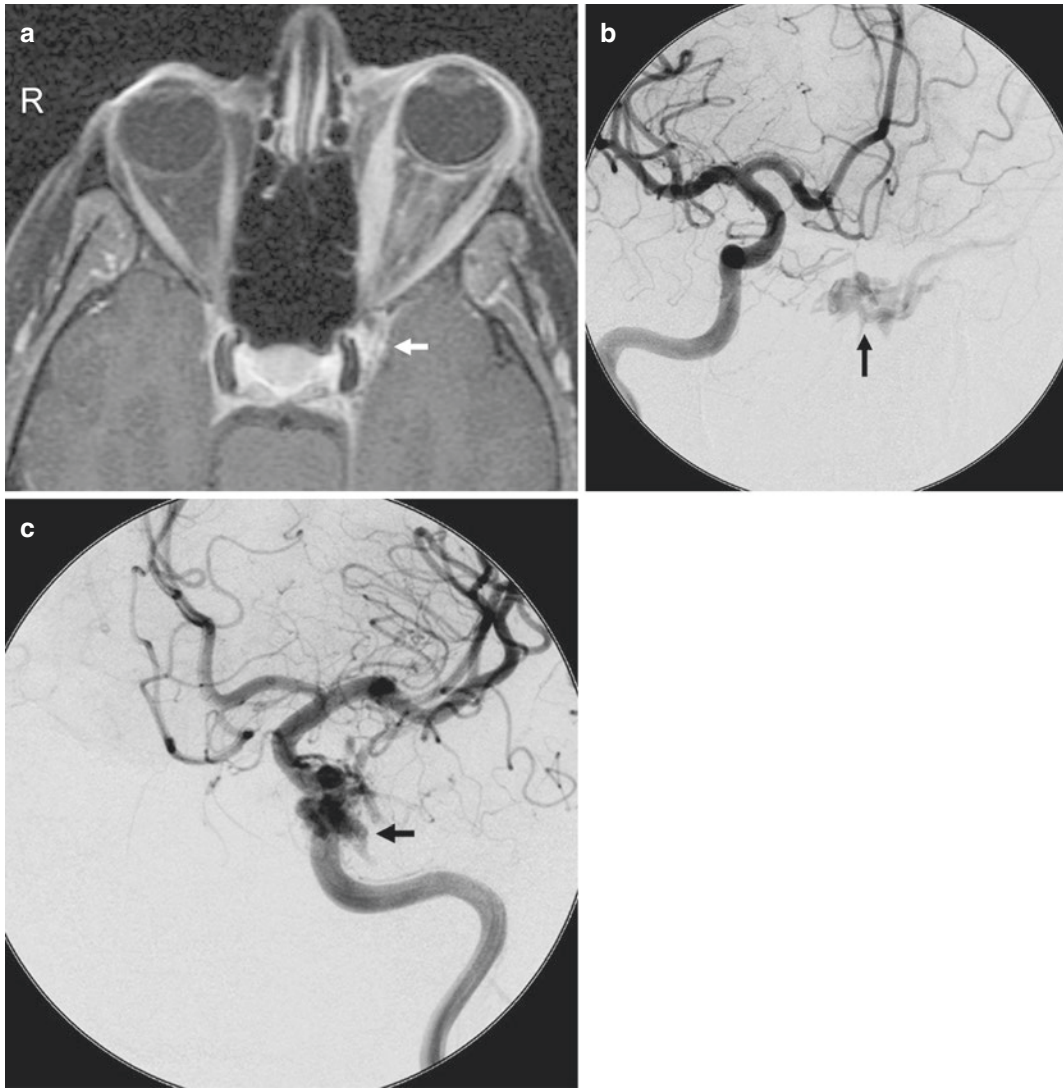

Fig. 24 Left CCF. (**a**) Axial T1-weighted post-contrast with fat suppression image demonstrates left proptosis, enlargement of the left extraocular muscles, and slight asymmetric fullness of the left cavernous sinus. (**b**, **c**) Catheter cerebral angiogram from selective right (**b**) and left (**c**) ICA injections shows abnormal filling of the left cavernous sinus, confirming a left CCF (*arrow*)

on CTA is a common radiological hallmark of a CCF. Direct CCFs are high flow shunts, and identification of the site of the communication between the internal carotid artery and cavernous sinus can be difficult on cerebral angiography. Contrast injection of the vertebral artery with compression of the internal carotid artery and balloon occlusion of the internal carotid artery together with manual aspiration from the balloon-guiding catheter have been reported as techniques to unmask the site of the shunt [138].

Patients can present with a CCF weeks or even months after the initial trauma. Therefore, a CCF can be easily overlooked, and a detailed clinical history and examination, including auscultation for a bruit and an ophthalmic examination, are important to follow-up in patients at risk for development of a CCF. Classic imaging features of the CCF include engorgement of the cavernous and petrosal sinuses and a dilated tortuous ipsilateral superior ophthalmic vein. When the supe-

rior ophthalmic vein exceeds 4 mm in diameter, a CCF should be suspected. Other imaging findings include enlarged extraocular muscles, proptosis, retrobulbar fat stranding, pre-septal soft tissue swelling, and an ipsilateral convex cavernous sinus. These findings may even be bilateral and symmetric because venous channels connect the cavernous sinuses. In severe cases, intracranial venous hypertension can lead to cortical venous reflux, brain edema, and hemorrhagic venous infarction.

The *dural arteriovenous fistula* (DAVF) is rarely identified as an acute traumatic lesion. However, laceration of the middle meningeal artery with resultant meningeal artery to meningeal vein fistulous communication has been detected by cerebral angiography in the acute TBI patient (Fig. 25a–d). Because the fistula

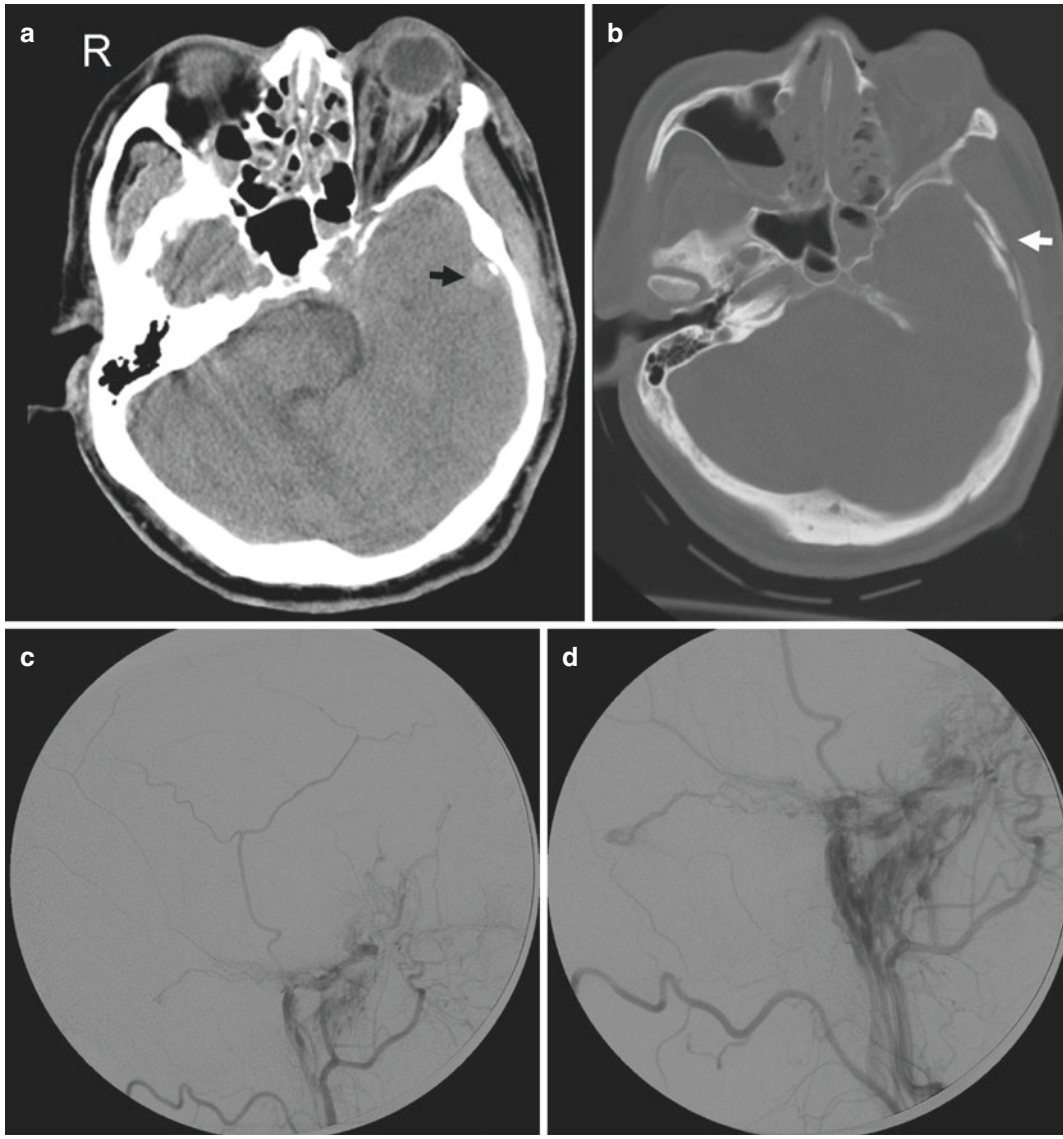

Fig. 25 Dural arteriovenous fistula (DAVF). (**a**) Axial CT image displayed in "soft tissue window" shows a small, round, dense, left temporal extra-axial focus (*arrow*). There is also left orbital proptosis and retrobulbar soft tissue stranding. (**b**) Corresponding "bone window" image shows a fracture of the squamosal portion of the left temporal bone (*arrow*). (**c, d**) Images from an external carotid artery catheter angiogram in the lateral projection show an abnormal blush of contrast due to a dural AVF with filling of the middle meningeal vein via the middle meningeal artery. (All: Reprinted with permission of John Wiley and Sons from Le and Gean [121])

generally drains via the meningeal veins, the injured middle meningeal artery rarely leads to the formation of an EDH. More frequently, DAVFs are detected in patients without an acute trauma history. Patients are often asymptomatic or present with nonspecific complaints, such as tinnitus. Thrombosis and occlusion of a dural venous sinus, with resultant venous hypertension, has been implicated as a possible underlying cause of DAVFs. The torcula and sigmoid sinuses are common sites of DAVFs. Trauma is a common cause of transverse and sigmoid sinus thrombosis and occlusion, raising the possibility that some DAVFs may be caused by remote traumatic venous injury.

Acute Secondary Injury

Cerebral Swelling

Cerebral swelling refers to an increase in cerebral volume which can develop from an increase in tissue blood volume (*hyperemia*) or an increase in tissue fluid (*cerebral edema*). Cerebral edema can be further divided into five major subtypes: vasogenic, cytotoxic, hydrostatic, hypoosmotic, and interstitial. Among these subtypes, vasogenic edema is the most common in TBI. Hyperemia and vasogenic edema are thought to be the result of cerebral dysautoregulation. Cytotoxic edema is believed to occur secondary to tissue hypoxia. Hydrostatic edema occurs from a sudden increase in intravascular pressure and can be seen with sudden decompression of a focal mass. Hypoosmotic edema is caused by a decrease in serum osmolality, with subsequent efflux of fluid from the intravascular to the extravascular space. Interstitial edema occurs from movement of fluid into the periventricular space secondary to obstructive hydrocephalus.

Effacement of the cerebral sulci and cisterns, as well as compression of the ventricles, is a typical imaging finding (Fig. 26). In cytotoxic edema, the gray-white differentiation is lost, in contrast to hyperemia and vasogenic edema where the gray-white differentiation is preserved. The cerebellum and brainstem are usually spared, even with cytotoxic edema, and may appear hyperintense relative to the affected cerebral hemispheres.

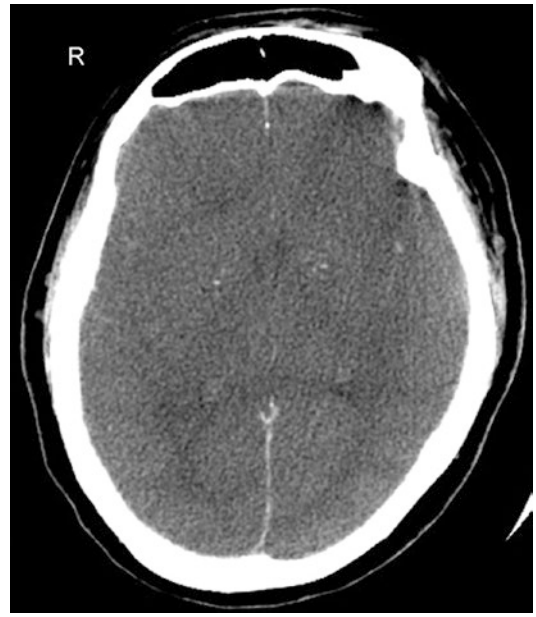

Fig. 26 Cerebral edema and TAI. Non-contrast axial CT image demonstrates diffuse effacement of the cerebral sulci and diffuse loss of gray-white matter differentiation due to diffuse cerebral edema. Multiple foci of shear hemorrhages within the left temporal lobe are also visible, indicating acute hemorrhagic TAI

Brain Herniation

Traumatic *brain herniation* refers to displacement of brain tissue from one compartment to another secondary to mass effect produced either by primary or secondary injuries. The compartmentalization is based on the dural partitions and skull openings. In *subfalcine* herniation, the cingulate gyrus is displaced across the midline under the falx cerebri and above the corpus callosum (Figs. 8b and 10a). Compression of the ipsilateral ventricle often manifests due to the mass effect, while the contralateral ventricle may be enlarged due to obstruction of the foramen of Monroe. In *uncal* herniation, the medial temporal lobe is displaced over the free margin of the tentorium. Effacement of the lateral aspect of the suprasellar cisterns is an important early clue indicating the presence of uncal herniation. In *transtentorial* herniation, the brain herniates either upward or downward through the tentorial incisura. Downward herniation of the cerebrum manifests as effacement of the suprasellar and perimesencephalic cisterns. Elongation of the midbrain

may be seen. Inferior displacement of the calcified pineal gland is another clue to the presence of downward herniation. Upward herniation occurs in the setting of trauma to the posterior fossa, when portions of the cerebellar hemispheres and vermis displace through the tentorial incisura. Mass effect in the posterior fossa often manifests with flattening of the pons and effacement of the prepontine and cerebellopontine cisterns. In *tonsillar* herniation, the cerebellar tonsils displace through the foramen magnum with compression of the lower brainstem. *External* cerebral herniation occurs in the setting of elevated ICP in combination with an open skull defect (Figs. 8b and 29b). External herniation is observed more frequently due to an increased use of surgical decompressive craniectomies. A large craniectomy enables the brain to externally herniate through the skull defect, without compressive effects on the brain tissue. By comparison, decompressive craniectomies performed with small skull openings often lead to compression of cortical veins against the bone edges and venous infarction of the externally herniated brain tissue [139]. With all types of brain herniation, the mass effect and raised ICP must be corrected in a timely fashion to prevent further secondary injury.

Ischemia and Infarction

Ischemia and infarction can result from vascular injury, a diffuse increase in ICP, cytotoxic cerebral edema, or focal compressive mass effect on the cerebral vasculature. With subfalcine herniation, the anterior cerebral arteries (ACA) may be compressed, leading to ACA infarction. In severe uncal herniation, displacement of the temporal lobe can compress the ipsilateral posterior cerebral artery, leading to infarction in the downstream territory of the occipital lobe. Uncal herniation may also compress the contralateral cerebral peduncle against the tentorium ("Kernohan's notch"), leading to peduncular infarction. Tonsillar herniation can cause ischemia in the territory of the posterior inferior cerebellar artery.

Chronic Secondary Injury

Hydrocephalus

In the acute TBI setting, mass effect with brain herniation can cause intraventricular obstruction (*non-communicating hydrocephalus*) via compression of the aqueduct, foramen of Monroe, or ventricular outflow foramina. Dilation of the ventricular system upstream of the site of obstruction is readily detected on imaging. In these settings, a ventriculostomy is inserted for the temporary management of the hydrocephalus. Rarely is a permanent ventricular peritoneal shunt required in the management of acute TBI. Traumatic *hydrocephalus* more commonly develops in the subacute or chronic period due to impaired CSF reabsorption at the level of the arachnoid villi (*communicating hydrocephalus*). A delayed complication of prior traumatic SAH or IVH, communicating hydrocephalus appears on imaging as uniform enlargement of all ventricles. The sulci may be effaced and periventricular transependymal interstitial edema may also be evident. A ventriculoperitoneal shunt may be necessary to manage communicating hydrocephalus.

Cerebrospinal Fluid Leak

Cerebrospinal fluid (CSF) leak occurs from a dural tear and an associated skull base fracture. The dural tear results in communication between the intra- and extradural spaces. Communication between the subarachnoid space and middle ear, in association with a ruptured tympanic membrane, causes CSF otorrhea. Similarly, communication between the subarachnoid space and the paranasal sinuses causes CSF rhinorrhea. In patients with recurrent meningeal infections and a history of trauma, an occult CSF leak should be suspected. CSF leaks are often difficult to localize. CT imaging with high-resolution cuts through the anterior skull base or temporal bone may be used to identify the site of the CSF leak [140, 141]. If these studies fail to conclusively identify the presence and site of a CSF leak, radionuclide or CT cisternography studies may be employed [2]. Radionuclide cisternography is

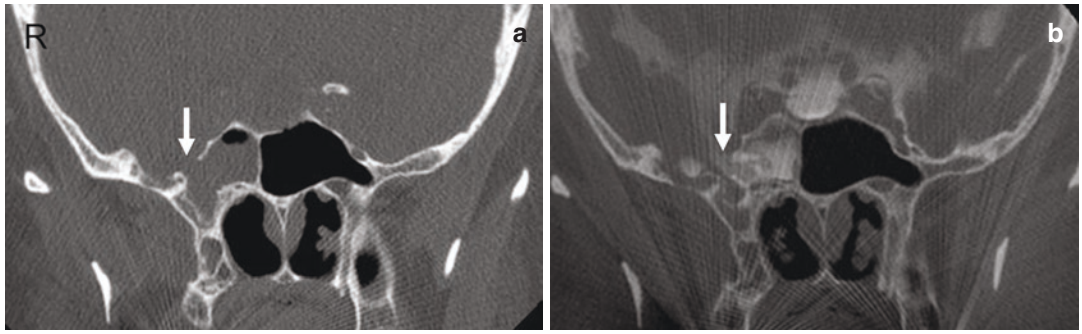

Fig. 27 CSF leak. (**a**) Coronal CT image shows a bony defect of the right sphenoid sinus (*arrow*). (**b**) Coronal CT image from a cisternogram shows leakage of contrast into the right sphenoid sinus through the bony defect. (Both: Reprinted with permission of John Wiley and Sons from Le and Gean [121])

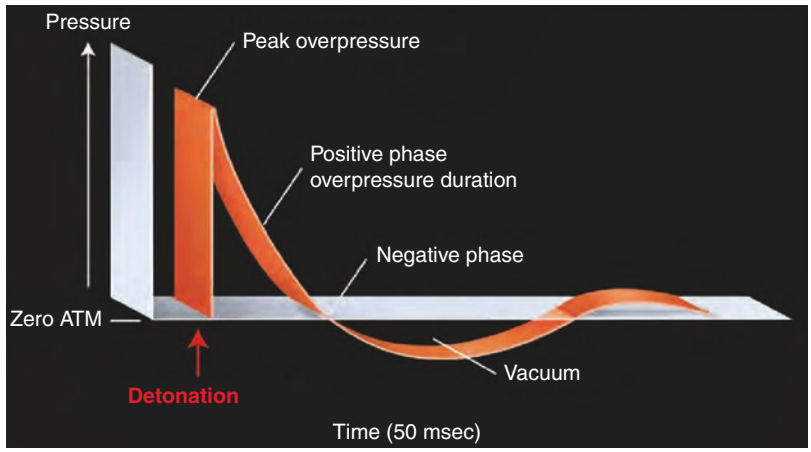

Fig. 28 Idealized blast pressure waveform. Explosions consist of a blast wave that has two components: an initial high-pressure shock wave front that compresses the surrounding air and a subsequent negative pressure phase. This later drop in atmospheric pressure (ATM) below normal creates a relative vacuum that causes air to be drawn back toward the point of detonation. The blast waveform shown is called *idealized* because explosions usually occur in complex spaces like those found in an urban environment. As a result, shock waves reflect off surfaces and interact with each other in highly variable ways. (Reprinted with permission of Wolters Kluwer from Gean [152])

highly sensitive for the detection of a CSF leak [142]; however, it does not precisely localize the leak. CT scanning with intrathecal contrast may be required for detailed anatomic localization of the defect (Fig. 27a, b) [143].

Blast-Induced Injury

Blast-induced TBI is brain injury generated by an explosion. Blast-induced TBI is the signature wound of the Iraq and Afghanistan wars due to the expanded use of improvised explosive devices (IEDs) in terrorist and insurgent activities [108, 144]. Blast injuries can be classified as *primary, secondary, tertiary, or quaternary*. *Primary blast injuries* are due to the propagation of high- and low-pressure shock waves through the tissue (Fig. 28). The brain parenchyma, surrounded by cerebral fluid, is especially susceptible to primary blast injury. *Secondary blast injuries* are penetrating injuries caused by projectiles arising from explosive devices and other objects propelled by the explosion. *Tertiary blast injuries* result when a person becomes a missile and is thrown against other objects. Therefore, tertiary blast injuries are

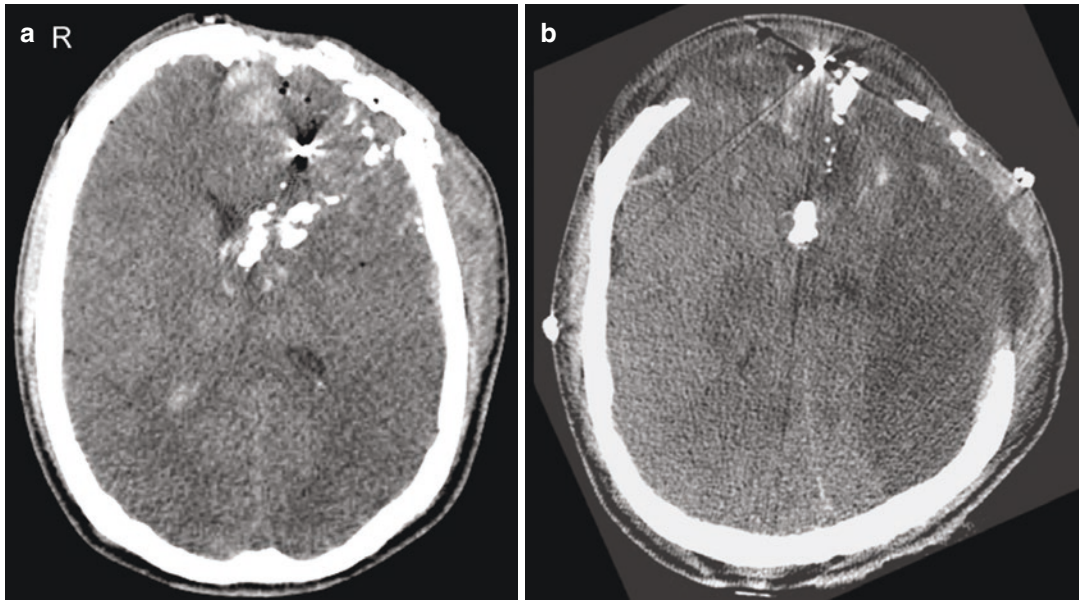

Fig. 29 Blast-induced TBI. (**a**) Non-contrast axial CT images show multiple metallic fragments, comminuted left frontal fractures, left frontal pneumocephalus, and left frontal scalp soft tissue swelling. High-density collection within the occipital horn of the right lateral ventricle indicates acute IVH. (**b**) Follow-up CT, performed after decompressive craniectomy, reveals left frontal external herniation. There is diffuse decrease in attenuation of the left frontal lobe and loss of gray-white differentiation from secondary ischemic injury. There is also diffuse effacement of the cerebral sulci from cerebral edema. Bilateral anterior frontal low attenuation also indicates ischemic changes in these regions

similar to those that occur in blunt trauma, with acceleration and deceleration injury and impact forces as the main mechanisms of trauma. *Quaternary blast injuries* are all other injuries not included in the first three classes, including thermal and inhalation injuries. The manifestation of blast injury on the brain is usually a combination of the different classes of blast injury (Fig. 29a, b). Brain injuries due to explosions often develop cerebral edema, subarachnoid hemorrhage, and vasospasm (Fig. 30a, b).

Summary

Diagnosis and management of TBI requires a multidisciplinary approach. The goals of imaging in TBI involve identifying treatable injuries, assisting in the prevention of secondary damage, and providing useful prognostic information. While progress in medical imaging technology has resulted in an increase in multiple imaging methods, leading to improvement in early detection of TBI and adding useful prognostic information, CT still remains the workhorse imaging modality in the acute setting. CT is fast and widely accessible and has few contraindications. MRI is indicated in the acute setting if the neurologic findings are unexplained by the CT imaging. MRI is preferred over CT for subacute and chronic TBI because of its superior sensitivity to older blood products and to both gray and white matter injury. Novel MRI methods, such as DWI, SWI, DTI with tractography, MRS, MTI, and perfusion MRI, further improve the sensitivity of MRI in detecting TBI lesions and add to our understanding of TBI. PET and MSI show promise in the evaluation of TBI, although their availability is limited due to cost. Each one of these techniques has its advantages and limitations. A combination of these advanced techniques – multimodality imaging – is probably the best way to enhance accurate detection of TBI that cannot be detected by conventional MRI or CT. Continuing

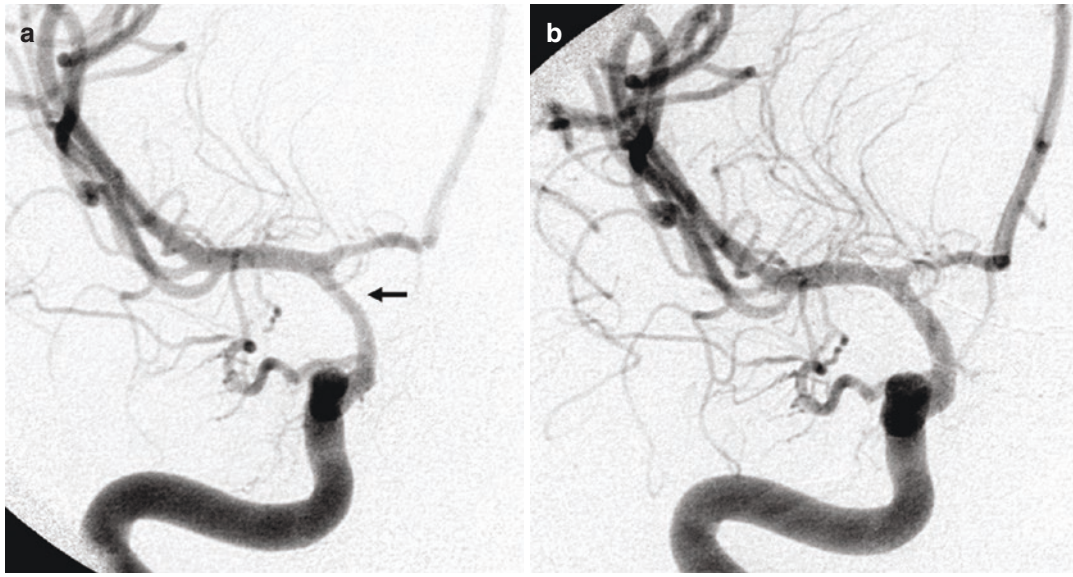

Fig. 30 Blast-induced vasospasm pre- and post-angioplasty. (**a**) Catheter cerebral angiogram from a selective left ICA injection of the same patient in Fig. 29 shows mild narrowing and irregularity of the supraclinoid left ICA (*arrow*) due to vasospasm. (**b**) Follow-up angiogram post-angioplasty shows improvement in the irregularity and narrowing. (Courtesy of Rocco Armonda, MD, Washington Hospital Center, Washington, DC.)

research and development in imaging will continue to improve our understanding of the pathophysiology of brain trauma and our clinical management of TBI patients.

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Neuropsychological Assessment of mTBI in Adults

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Introduction

Mild traumatic brain injury (mTBI) refers to a wide range of brain injuries that are considered to be at the milder end of the TBI severity spectrum. mTBI has been classified as those injuries that result in a Glasgow Coma Scale (GCS) score of 13–15, a duration of loss of consciousness (LOC) of less than 30 minutes, and duration of post-traumatic amnesia (PTA) of less than 24 hours (Tables 1 and 2). PTA has been reported as a more effective measure of severity of mTBI than GCS in the context of predicting behavioral outcomes at 6 months post-injury [1]; however, the challenges of reliably assessing PTA in relation to mTBI is highlighted by Ruff and colleagues [2]. Even where there is an absence of PTA and/or LOC, cognitive abnormalities may be detected in the immediate aftermath of a suspected concussion [3].

Table 1 Traumatic brain injury classification (civilian)

TBI severity	Classification criteria[a]		
	LOC	PTA	GCS
Mild	≤30 minutes	<24 hours	13–15
Moderate	30 minutes to 1 week	24 hours to 1 week	9–12
Severe	>7 days	>7 days	≤8

Note: *GCS* Glasgow Coma Scale Score, *LOC* duration of loss of consciousness, *PTA* duration of post-traumatic amnesia

[a]Data from Ref. [15]

mTBI is a common occurrence and is considered to be a major public health issue globally. The annual worldwide incidence has been estimated at 45 million [4], with over one million in the United States alone [5]. This estimate is known to be conservative as there is an absence of data on individuals suffering a mTBI who do not present to hospital, and those who do present, but are discharged at the emergency department (ED) [6]. Between 70% and 80% of all TBIs are classified as mild [7], but despite this, these injuries can be a continuing cause of disability, leading to cognitive, mood, and behavioral disorders [8]. For many people, post-injury symptoms usually resolve within days or weeks. Yet for a substantial

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Table 2 Veteran Health Administration and Department of Defense TBI Classification Scheme

TBI severity	Classification criteria				
	LOC	Alteration of mental state	PTA	GCS	Structural imaging
Mild	0–30 minutes	A moment up to 24 hours	0–1 day	13–15	Normal
Moderate	30 minutes to 1 week	>24 hours, severity based on criteria	1–7 days	9–12	Normal or abnormal
Severe	>24 hours	>24 hours, severity based on criteria	>7 days	≤8	Normal or abnormal

Note: Alteration of consciousness/mental state must be immediately related to the head
GCS Glasgow Coma Scale Score, *LOC* duration of loss of consciousness, *PTA* duration of post-traumatic amnesia

minority of individuals with mTBI, intracranial abnormality (referred to as "complicated" mTBIs) may be detected on computed tomography (CT) [9], with prevalence rates varying from 5% [10] to approximately 40% [11] between various studies [12]. Slow recovery (where symptoms persist beyond the initial weeks or months post-injury) occurs in 5–20% of mTBI individuals. These cases are referred to as suffering from persistent post-concussion syndrome (PCS) [13]. The provenance of such ongoing problems is controversial [14].

Etiology

A TBI may occur from any number of causes and may vary according to gender, age, race, and geographical location. Falls have been reported as the leading cause of TBI, accounting for two in every five TBIs. Of individuals over 64 years, 81% of TBIs were a result of a fall, while in children under the age of 15 years, falls accounted for 55% of TBIs [4].

Incidence Rates

The incidence of mTBI (approximately 131 cases per 100,000 people) far exceeds that of moderate TBI (15 cases per 100,000 people) and severe TBI (14 cases per 100,000 people) [15, 16].

Definitions of Mild Traumatic Brain Injury and Persistent Concussion Symptoms

There are various terms used, often interchangeably, for the type of injury and subsequent symptoms associated with mTBI and PCS. In this chapter, the term mTBI will refer to the initial injury, and PCS will refer to persistent post-concussion symptoms following such injury (over weeks, months, and years). Immediate physical symptoms of mTBI may include headache, dizziness, nausea, unsteady gait, slurred speech, and cognitive signs, such as confusion or disorientation, reduced processing speed, memory disturbance, concentration difficulties, and executive dysfunction [17]. A LOC (e.g., GCS score of 13 or above) is considered a mild injury. However, amnesia, especially PTA, has been proposed as either an additional or an alternative diagnostic criterion to LOC, in conjunction with confusion [18]. Gradations of mTBI severity have been recommended in the past by the American Academy of Neurology [19, 20].

Post-concussion Symptoms

There are numerous post-TBI self-report symptom inventories available to record subjective symptoms and the degree of impact or level of severity each endorsed symptom is having on an individual (e.g., Rivermead Post Concussion Symptoms Checklist [21], Concussion Signs and Symptoms Checklist). Residual signs and symptoms of sport-related concussion and mTBI may include those outlined in Table 3. In sport-related concussion, the large majority of athletes self-report resolution of symptoms within 7–10 days, and certainly within 1 month post injury [22]. This pattern of acute disturbance and recovery is remarkably consistent with the pattern of physiological disturbance and recovery described in neuroscience research [23, 24].

PCS is not a single pathophysiological entity. It is a term used to describe a constellation of non-specific symptoms (e.g., memory disturbance,

Table 3 Common signs and symptoms of mild TBI and sport-related concussion

Cognitive	Physical	Emotional/mood	Sleep disturbance
Difficulty thinking clearly	Headache	Irritability	Sleeping more than usual
Difficulty remembering	Nausea/vomiting	Feeling more emotional	Sleeping less than usual
Difficulty concentrating	Neck pain	Sadness	Trouble falling asleep
Feeling slowed down	"Pressure in the head"	Anxiety	
Feeling like "in a fog"	Balance problems	Nervousness	
"Don't feel right"	Dizziness		
Confusion	Sensitivity to noise		
Drowsiness	Sensitivity to light		
	Blurred vision		
	Fatigue, lacking energy		

difficulty with concentration, irritability, anxiety, depression, apathy, headache, fatigue, sleep disturbance, balance problems, visual disturbance, sensitivity to light and/or noise) that are linked to several possible causes that do not necessarily reflect ongoing physiological brain injury [25]. The differential diagnosis of PCS includes depression, somatization, chronic fatigue, chronic pain, vestibular dysfunction, ocular dysfunction, or some combination of these conditions [26].

For the clinician, the challenge is to determine whether prolonged symptoms after mTBI reflect a prolonged version of the concussion pathophysiology as opposed to a manifestation of a secondary process, such as premorbid clinical depression or migraine headaches [27, 28]. Obtaining a prior medical history, performing a careful physical examination, and considering the response to physical or mental exertion (i.e., whether exertion reliably exacerbates symptoms) [29] when developing the differential diagnosis of persistent post-concussion symptoms are essential. This process may enable the clinician to link symptoms of post-concussion "syndrome" to one or more definable post-concussion "disorders" [30]. For example, establishing a pre-morbid history of migraine headaches, depression, anxiety, attention deficit hyperactivity disorder, or learning disability is crucial because mTBI can exacerbate these conditions, and they, in turn, can be responsible for ongoing symptoms [28]. It has been noted that a strong vulnerability factor in the development of PCS is older age compared to those typically presenting with milder head injury and that female gender is significant [31].

For determining PCS, there are the International Classification of Diseases (ICD) section F07.2 (post-concussional syndrome) diagnostic criteria. The controversy regarding the validity of post-concussional disorder is reflected in the latest version of the Diagnostic and Statistical Manual of the American Psychiatric Association (i.e., DSM-V) [32]. There is no longer a category for post-concussional disorder, but a new disorder category known as the "neurocognitive disorders." Within the spectrum of neurocognitive disorders is a new category (i.e., "Major or Mild Neurocognitive Disorder due to Traumatic brain Injury"). There is reference to different categories of TBI, including mild, moderate, and severe. Neurocognitive symptoms associated with mTBI are noted to resolve within days to weeks after the injury, with complete resolution by 3 months (DSM-V). It is not known yet whether the next version of the ICD will revise the diagnostic category of PCS. The specific DSM-V criteria for neurocognitive disorder due to TBI are as follows:

1. The criteria are met for major or mild neurocognitive disorder.
2. There is evidence of a TBI—that is, an impact to the head or other mechanisms of rapid movement or displacement of the brain within the skull, with one or more of the following:
   - LOC
   - PTA
   - Disorientation and confusion
   - Neurological signs (e.g., neuroimaging demonstrating injury, a new onset of seizures, a

marked worsening of a preexisting seizure disorder, visual field cuts, anosmia, hemiparesis)
3. The neurocognitive disorder presents immediately after the occurrence of the TBI or immediately after recovery of consciousness and persists past the acute post-injury period.

Consequences of mTBI/PCS

mTBI is "classically defined as an essentially reversible syndrome without detectable pathology" [33]. It is often noted that recovery following mTBI is rapid—with most acute symptoms resolving within hours, and then, typically, a person being symptom-free by around 10 days [22].

Typically, the more severe injuries occur from greater rotational acceleration–deceleration forces involved in the impact [34]. Following impact, a neurometabolic cascade ensues [24]. The short-term effects can include a lack of electro-chemical activity, hemorrhaging, and axonal shearing, especially in the frontal temporal lobe area, although in mTBI these early deficits may largely resolve themselves [35]. mTBI, therefore, tends to be characterized by dysfunction or neurobehavioral profile rather than underlying neuropathological changes [36]. Caution, though, is still warranted regarding signs of greater impact.

Considerations Regarding Neuropsychological Testing

The common cognitive domains typically affected by mTBI include executive functions (a set of cognitive abilities that control and regulate volitional activities, such as planning, organizing, self-awareness, impulse control, mental flexibility, problem solving, and other self-regulatory functions), information processing speed (the speed, or how quickly, cognitive tasks are performed), sustained attention (the ability to maintain consistent behavioral responses over time to specific stimuli during an ongoing repetitive task), divided attention (the ability to respond to two or more different tasks at the same time), and memory (the ability to encode, store, and retrieve information within various time frames from the original encoding experience).

There are two main reasons for neuropsychological assessment for concussion: (i) to determine the presence of cognitive symptoms for early diagnosis of mTBI (in terms of severity and potential duration of injury) and (ii) to monitor recovery over days, weeks, months, or even years later [37, 38]. In the latter, there may be identification of lasting neuropsychological sequelae.

Neuropsychological testing needs to be specific, sensitive, reliable, and valid for identifying mTBI/PCS [39]. Validity is the accuracy of the measurement or the extent to which the test is measuring what it is purported to be measuring. Sensitivity and specificity refer to the likelihood of identifying either genuine positives or negatives, respectively. Sensitivity is the probability that someone in the category of interest (in this case, mTBI) is identified by the test. Conversely, if a test has a high level of specificity, it will reliably predict those who do have the condition versus those who do not have the condition. Reliability refers to the consistency of the measurement or the extent to which the test provides approximately the same result on each occasion it is used under the same set of conditions with the same participants.

Test–retest reliability is also an important consideration in view of the potential for serial assessment post-injury to track recovery trajectories. A large body of work has considered test–retest reliability at various intervals [40–46]. Recently Maerlender and colleagues [47] examined four sequential time points for the Immediate Post-Concussion Assessment and Cognitive Testing (ImPACT) computerized battery and reported that the two memory composite scores increased significantly with successive administrations.

For further review on advanced topics in neuropsychological assessment following sport-related concussion, see Iverson and Schatz [48]. Some of these topics are discussed below.

Baseline and Post-injury Assessment

At-risk populations, such as athletes of full contact and collision sports and military service members, are unique populations that offer the opportunity to employ a baseline (i.e., pre-injury exposure) post-injury model.

When considering cognitive tasks to use in a baseline (pre- and post-injury) model, test–retest reliability is especially important. This can be estimated by comparing the results of a test on the same population carried out at different times—e.g., using a correlation coefficient. However, such repeat testing can lead to practice effects, whereby the participant performs better in subsequent tests due to having "learned" from the previous experience [49].

Where it is known that if a test is susceptible to practice effect, then Reliable Change Indices (RCI) can be used to calculate what improvement would be expected from a person from baseline to post-concussion testing and what adjustment is needed to take account of such expected improvement [50]. The RCI is calculated by use of a control group to establish the average change between tests, and an additional correction is made for test variability and reliability using an error term which produces a standard score (*Z*). Furthermore, use of alternate versions of tasks can limit practice effects [51].

A number of studies have reported on reliable change, sensitivity, and predictive value for the commonly used ImPACT battery. Van Kampen and colleagues [52] reported 83% of concussed athletes had at least one ImPACT score that exceeded the reliable change index for that score, compared to 30% of the control group. Sensitivity was reported to increase by 19% with the addition of ImPACT result to a post-concussive symptom questionnaire. The predictive value of ImPACT, where at least one abnormal composite score was evident, was 83%, and the predictive value of a negative test result was 70%. Overall, 93% of concussed athletes were correctly identified as concussed when the post-concussive symptoms score, and at least one ImPACT score were determined to be abnormal [52]. The combined sensitivity of ImPACT and the concussive symptoms score in high school athletes has been reported at 89% and specificity at 82% [53]. Results suggest the ImPACT battery may be sensitive to the effects of sport-related concussion once subjective symptoms have resolved [52, 54, 55]. Being cognizant of false-positive rates of RCIs for concussion batteries is also an important reference point that can assist with interpretation of RCI output for multi-test batteries. For example, the majority of normal individuals would be expected to demonstrate significant declines on at least one RCI for batteries producing seven or more uncorrelated RCIs (80% confidence intervals), although expected rates are lower for tests with fewer indices, higher inter-RCI correlations, and more stringent impairment criteria [56].

The baseline post-injury model in at-risk populations (e.g., athletes and military service members) is vulnerable to "sandbagging" (incomplete effort) at baseline, and, as such, inbuilt measures of effort are incorporated in the neuropsychological test design. The motivation for intentional poor performance on baseline is to appear to be "recovered" post-injury and, therefore, able to return to activities sooner. The frequency of poor effort on baseline testing has been reported as 9% [57] to 11% in high school athletes [58], 6% in a collegiate sample [59], and 6% in a sample of US National Football League (NFL) players [60]. Intentional (or motivated) poor performance has been reported to be difficult on the ImPACT test, with one study reporting that only 11% of test takers were able to successfully underperform without detection from the inbuilt integrity measures [61].

When no initial baseline is available, it is still possible to consider reliable change post-mTBI, but such approaches are in early development. Through the use of intra-individual measures of quotients that are unlikely to be adversely affected by mTBI, analysis of test scores generated from neuropsychological assessment at the individual level can be used. Correlation coefficients that exist between tests may be utilized,

together with the *z*-score distribution to undertake statistical analyses. Using standard error estimates, it is possible to calculate the probable range of scores that a person would have in testing, with scores falling increasingly further from the predicted range being increasingly improbable. Such discrepancy analyses are already available in analyses of discrepancies between WAIS-IV indices, for example, based upon these tests being co-normed. The approach advocated here facilitates such analyses between non-co-normed tests, which the authors are developing.

Clinical Management of At-Risk Populations

There is a strong literature that has developed over a number of decades pertaining to athletes involved in full-contact and collision sports and concussion. The literature on mTBI and neuropsychological testing is dominated by studies conducted in populations engaged in sports activities. Studies with military populations have garnered considerable research attention, due in large part to the level of involvement of military forces from many nations in the Afghanistan and Iraq wars.

Neuropsychological assessment and management models in at-risk populations are designed to promote the screening of large numbers of people in order to establish an individual standard for each person. The model is distinctly different from more traditional models of neuropsychological evaluation that utilize extensive, thorough (but time-consuming) test batteries. The baseline evaluation is not meant to represent a comprehensive assessment, but is targeted to assess cognitive domains that are most often affected by mTBI/concussion, such as memory, attention and concentration, executive function, speed of mental processing, and reaction time [62]. It has been proposed that the most effective use of neuropsychological test data to help determine post-injury return to activity occurs by obtaining a "baseline" level of function prior to sustaining an injury [63]. Baseline testing is typically conducted at pre-season training camps for athletes and incorporated into the routine pre-deployment preparations for the military. Individuals who are suspected of sustaining a concussion are then retested (the timing of the post-injury testing will be contingent upon the clinical question). It is considered standard practice that an individual's cognitive performance must return to baseline or better, prior to recommencing regular (at-risk) activities, in order to avoid the possibility of re-injury prior to making a full recovery [62, 64]. Determining cutoff scores in neuropsychological performance and post-concussion symptom clusters for classifying protracted recovery in concussed athletes may assist in setting numerical thresholds for clinicians to predict recovery [65].

Military-Related mTBI Studies

Military service members are another at-risk group for sustaining mTBI/concussion. Cognitive complaints in military service members following combat exposure are common, particularly in individuals who have sustained mTBI, with some 15–20% of military service members reporting a history of mTBI [66]. TBI as a result of combat action may occur from blast injury, penetrating head injury, or via other non-blast exposure. The ongoing development of military armor for use in combat and the more common use of improvised explosive devices on the battlefields of modern conflicts has led to an increase in exposure to blast-related injury. The effects of blast-related mTBI on behavior and cognition continue to be a controversial topic.

In a study examining clinical outcomes in US military personnel with blast-related versus non-blast-related TBI, neuropsychological outcomes (together with global outcomes, headache severity, depression, and PTSD) were not found to be significantly different between the two groups, although both groups had higher rates of moderate to severe overall disability than the respective control groups [67]. Another recently published study reported that US Marines who sustained a concussion during a combat deployment had more post-deployment symptoms than Marines

who were exposed to explosive blasts who, in turn, reported greater numbers of clinical symptoms than Marines who were not exposed to blasts and did not sustain a mTBI/concussion during the deployment [68].

A recent meta-analysis of the cognitive outcomes of blast-related mTBI found that executive function (specifically, set-shifting), delayed memory, and information processing speed were the most sensitive cognitive domains affected by blast-related mTBI [69]. Interestingly, post-traumatic stress disorder (PTSD) was not found to be a significant moderator in predicting cognitive effects sizes [69]. Lange and colleagues [70] found that there were no significant differences when comparing the neuropsychological outcome in US military service members suffering from uncomplicated mTBI, complicated mTBI, and moderate TBI, within the previous 6 months. In another sample of US military service members who had sustained a mTBI, the self-reported cognitive complaints were not found to be associated with neuropsychological test performance, but were associated with psychological distress [71]. In an examination of neuropsychological profiles of US military populations, military personnel reporting "brain injury with current symptoms" were two times more likely to function at below average levels compared to those reporting "no previous TBI" [72].

Sport-Related Concussion Studies

An increasing awareness of the effects of sport-related concussion on cognition has led to sports physicians seeking fast and accurate assessment of cognitive function to facilitate management decisions about time of recovery and resumption of participation in sports. In a number of high profile sports, these are now done on the sidelines and may dictate return-to-play (RTP). Neuropsychological testing has been recognized as a unique and invaluable method for not only assisting with assessment of post-mTBI sequela, but also in tracking recovery over time [63].

Neuropsychological testing, the domain of the neuropsychologist, typically involves the administration of a variety of tests assessing cognitive abilities. The interpretation of neuropsychological test data assists athletes by identifying and tracking post-concussion symptoms and cognitive sequelae, lending valuable information for managing RTP decisions and focusing on the best interests of the athlete. Results of these tests, coupled with other clinical information (such as medical history, neuroimaging, and interviews with family members), give credence to the neuropsychologist for making important clinical and diagnostic decisions pertaining to disorders of the central nervous system [73]. The aim of neuropsychological assessment with respect to concussive injury is to detect and quantify residual cognitive and behavioral deficits [62].

The utility of neuropsychological testing in assessing concussion was proposed as early as the 1880s [74] and has been documented empirically since the early 1980s [75]. The development of sport-related neuropsychological testing occurred concurrently in both North America and Australia at this time. Barth and colleagues at the University of Virginia in the late 1980s [76] demonstrated the potential usefulness of neuropsychological testing to monitor and document cognitive recovery in the first week following a sport-related concussion. Although this pioneering work was the foundation for the field of neuropsychology to contribute to sport-related concussion, this project initially did not result in the widespread adoption of neuropsychological testing. In the early 1990s, a series of events transpired that promoted the use of neuropsychological testing of athletes in the clinical arena. Initially, concussive injuries to a number of high profile professional athletes resulted in implementation of baseline neuropsychological testing by several NFL teams. Almost immediately following this, the US National Hockey League (NHL) mandated baseline neuropsychological testing for every athlete subsequent to career ending injuries of a number of elite athletes. Coincident with this trend was the publications of several large-scale studies of collegiate athletes [77]. These studies provided further support for the implementation of neuropsychological testing of athletes suspected of sustaining a concussion.

Specifically, neuropsychological testing allowed individual baseline and post-injury analysis of the subtle aspects of cognition likely to be affected by sport-related concussion. Neuropsychological testing is now widely regarded as a valid clinical strategy for assessing the cognitive sequelae of sport-related concussion [62, 78–80].

Recovery from Sport-Related Concussion

The general consensus within the field of sports medicine is that isolated concussions in sports are often self-limiting injuries that are not associated with long-term cognitive or neurobehavioral problems [55, 81–83]. Most neuropsychological deficits appear to resolve within 10 days following a concussion [84, 85]. Studies from the sports concussion literature have shown that age [86], gender [87–89], learning disability/attention deficit disorder [78, 84], headache status, concussion history [80, 90–93], sleep and vigilance [94], and demographic and biopsychosocial factors [60] may have effects on baseline and post-concussion neuropsychological performances. For this reason, among others, the interpretation of neuropsychological test data should be conducted by a clinical neuropsychologist who is uniquely qualified to translate the test data into recommendations for clinical management [62].

Neuropsychological Impact of mTBI

Belanger and colleagues [95] conducted a meta-analyses reviewing the neuropsychological impact of mTBI across nine cognitive domains (an analysis that included 39 studies comprising 1463 mTBI cases and 1191 controls). The overall effect of mTBI on neuropsychological functioning was moderate ($d = 0.54$), with findings moderated by cognitive domain, time since injury, patient characteristics, and sampling methods. Mild neuropsychological impairments across domains were observed within the first 90 days, with specific and relatively large deficits in fluency ($d = 0.89$) and delayed memory recall ($d = 1.03$). However, by 90 days post-injury, no individual cognitive domain was found to be significantly different from zero ($d = 0.04$). In contrast, clinic-based samples and samples including participants in litigation were associated with greater cognitive sequelae of mTBI ($d = 0.74$ and 0.78, respectively) at 3 months or longer after the injury. Participants in litigation had an overall acute effect size ($d = 0.52$ at <90 days since injury) compared to unselected samples ($d = 0.63$). However, overall the results of this meta-analysis suggest that for the mTBI sample (unselected sample at large), there is full neuropsychological recovery by 3 months post-injury.

Conventional "Pencil and Paper" Neuropsychological Tests

Initially, neuropsychological testing was conducted on athletes and military personnel using pencil and paper measures [76, 84]. Many individuals suffering from mTBI have neuropsychological decrements detectable using conventional paper–pencil neuropsychological tests in the initial hours, days, and potentially weeks post-injury [63, 96–107]. The primary focus of the initial research examining cognitive function following sport-related concussion tended to relate to retrograde amnesia and memory retention [108]. The results indicated that athletes developed progressive retrograde amnesia and memory difficulties approximately 3–20 minutes after a concussion. Despite this relative success in detecting cognitive deficits, it became apparent that only assessing memory-related performance was not an effective way to evaluate the multi-dimensional cognitive sequelae typically observed following a sport-related concussion. As a result, the early focus on memory was expanded in subsequent studies to include multiple cognitive domains, including processing speed, reaction time, attention, and concentration as well as complex problem solving [76]. Concussed athletes were found to consistently perform poorly on these multidimensional neuropsychological tests [37, 76].

Deficits in speed of information processing or psychomotor speed are also apparent [109], and a number of pencil and paper tests have been developed specifically examining this neuropsycho-

logical construct [35]. Thus, mTBI testing batteries routinely incorporate at least one measure of processing speed [109]. The tasks frequently employed in "pencil and paper" testing include tests, such as Digit Span [110] which tests working memory with mental rotation, Speed of Comprehension and Language Processing [110] which tests general cognitive level and speed of processing, Trail-Making Tests A and B [110] which test sustained and divided attention, Stroop Color and Word [110] which tests executive skills (especially inhibition), and Symbol Digit Modalities Test (SDMT), a measure of visual-spatial and motor speed and accuracy [111].

The perceived value of neuropsychological testing for assessing and managing sport-related concussion was highlighted by the implementation in late 1990s of pencil and paper neuropsychological testing protocols in all NHL and the majority of NFL franchises. Such data were used extensively to determine more objective and individualized RTP parameters in athletes sustaining a concussion [64]. The Concussion in Sport group has endorsed neuropsychological testing as "one of the cornerstones of concussion evaluation and contributed significantly to both understanding of the injury and management of the individual" [96].

Conventional pencil and paper methods, however, were originally designed to examine gross impairment at a single point in recovery. That is, they were not designed to be serially administered to detect the very minor deficits in cognition often observed in sport-related concussion. Furthermore, conventional pencil and paper tests are time consuming and require trained, on-call clinical personnel to be properly administered [53, 112, 113]. This method of assessment may be feasible at the professional level. However, very few collegiate and high school programs have implemented this approach given the limitations of time, personnel, and finances [64].

Computerized Neuropsychological Tests

As a result of the inherent limitations of conventional pencil and paper neuropsychological tests and in parallel to the widespread proliferation of advanced technology, several researchers have developed computerized neuropsychological testing batteries and symptom evaluations as an alternative. These enable quick and efficient baseline evaluations of large groups of individuals [107, 114]. The use of comprehensive computerized neuropsychological batteries has largely supplanted the use of traditional neuropsychological measures in most concussion management programs [109]. Neuropsychological testing in the computerized format is considered to have several advantages and few limitations compared with conventional testing procedures. The documented advantages of this format of testing include:

- *Time efficiency* – The approach allows large numbers of athletes to be tested with minimal time and effort, promoting the testing of an entire team within a reasonable time period.
- *Easy storage of information* – Data collected from testing can be stored electronically (i.e., on the hard drive of the computer) and can be easily accessed at a later date.
- *More accurate measurement* – The use of a computerized format promotes more accurate measurement of cognitive processes, such as reaction time and information processing speed (the computerized format allows for accuracy to 0.01 of a second). This has inevitably resulted in an increase in the validity of detecting subtle changes in cognitive processes, particularly those related to speed of response.
- *Randomization* – The use of a computerized format allows for test stimuli to be randomized, which, in turn, should improve reliability across multiple administration periods, minimizing the practice effects inherent within multiple exposure to testing. Limiting the influence of practice effects on testing allows a direct interpretation of post-injury data with baseline performance of the athlete to determine whether or not full cognitive recovery has occurred.
- *Automatic scoring* – The computerized format allows for automatic scoring, eliminating the possibility for human error and enabling immediate feedback of the athlete's performance [63].

Table 4 Properties of conventional "pencil and paper" and computerized neuropsychological tests

	Conventional "pencil and paper" tests	Computerized tests
Psychometric considerations		
Alternative forms	None or very few	Infinite
Stimulus randomization	Within test only	Within test, between test and between subjects
Test–retest reliability	Wide range	Generally high for RT measures
Normative data	Mainly cross sectional, little LT	Very little for most tests
Practice effects	Large due to lack of alternative forms	Small: alternative forms and randomization
Output	Level of performance	Level of performance and variability
Practical considerations		
Administration time	1 minute–4 hours	1 minute–2 hours
Support required	NP or trained technician for admin	Self-admin and auto scored
Accessibility	Poor—requires a NP	High—may be internet delivered
Data storage and analysis	Time consuming and costly	Automated

NP neuropsychologist, *RT* response time, *LT* longitudinal, auto, automatic; admin, administration

In essence, a computerized approach appears to be more sensitive, reliable, practical, and certainly more cost-effective than conventional pencil and paper approaches. Because computerized neuropsychological testing is self-paced and self-directed, trained athletic trainers and other properly trained sports medicine staff members can administer baseline and follow-up tests [115]. However, this perceived advantage also has a distinct limitation, in that there is no real opportunity for the neuropsychologist to observe the athlete completing the test directly (i.e., qualitative information regarding the athlete cannot be collected and used for assisting with clinical decisions). See Table 4 for a summary of the properties of conventional "pencil and paper" neuropsychological testing and computerized neuropsychological testing.

There are a number of computer-based concussion management tools available or under development [116]. There are two with the largest share of the commercial market: ImPACT Applications® (San Diego, CA, USA) [117] and AxonSports (Scottsdale, AZ, USA; formally, CogState Ltd.'s CogSport©) [118]. An alternative test is commonly used by the US military (Automated Neuropsychological Assessment Metrics, or ANAM) [119]. A number of unique characteristics exist between these tests, and each is at a different stage of validation [116]. Each computerized battery has been developed to collect an individual baseline performance for comparison to post-concussive performance(s) should an athlete sustain a concussion during the season. As with conventional pencil and paper neuropsychological tests, issues pertaining to sensitivity, reliability, and validity of the respective options should be given careful scrutiny prior to implementation within the clinical setting [63].

Limitations of Neuropsychological Testing

Despite the accumulating evidence supporting the clinical utility of neuropsychological tests in this area, a number of limitations have also been documented [51, 115, 120]. A number of shortcomings of both conventional and computerized neuropsychological assessment tools have been highlighted, and the need for neuropsychological testing in managing mTBI has been challenged. A strong case has been put forth that neuropsychological testing contributes nothing when considering decisions related to return to activity and, therefore, the clinical benefit of such assessment has been questioned. In a sporting context, however, if an athlete is symptomatic, current guidelines do not permit RTP or resumption of training. In this context neuropsychological assessment provides the only current objective criteria to inform decisions around fitness to re-engage in a given activity.

There is a lack of support for the utility of neuropsychological tests in detecting residual neuropsychological impairments following more

obvious resolution of concussive symptoms, which is also problematic. This has further fueled the view that neuropsychological testing could not add clinical value to management and RTP decision-making. This is a moot point in the context of a recent review by Randolph, McCrea, and Barr [115], which highlighted that there are real risks involved in premature RTP that have never been clearly defined and, further, that no assessment technique or management intervention has ever been demonstrated that clearly attests to risk modification. As such, Randolph and colleagues did not endorse athletic teams allocating significant resources to implementation of an unproven method (neuropsychological testing) in an attempt to modify an unknown risk. In terms of the evidence for risks of sport-related concussion and the potential for risk modification from a neuropsychological perspective, prolonged recovery, same season repeat concussion, and late-life consequences, there is no current evidence to suggest that any specific guidelines or the use of baseline testing is of utility in modifying outcome from sport-related concussion [121].

While these criticisms may have some merit, we advocate that it is a narrow view to consider that neuropsychological testing has little value once symptoms have resolved. It is universally acknowledged that athletes are notorious at under reporting their symptoms following a concussion [122–126]; therefore, relying solely on the athlete's self-report, as is implied by this line of argument, is an unreliable management strategy that increases risk. Athletes may still be suffering from discrete residual cognitive deficits when reporting resolution of their post-concussion symptoms.

Subsequent to this critique, studies have found 38% of concussed athletes demonstrated impaired performance on at least one ImPACT variable following resolution of their symptoms [127]; a decline from baseline performance on divided attention scores on the CogSport battery has been reported in athletes no longer reporting symptoms; symptomatic and asymptomatic athletes examined on the CogSport battery following sport-related concussion demonstrated a significant decline from individual baseline performance in motor function and attention in symptomatic athletes. Further, there was a significant decline in divided attention in asymptomatic athletes [128].

Cognitive Function in mTBI and Neuroimaging

In over 90% of mTBI cases, CT and structural MRI investigations are unremarkable [129, 130]. However, with more sophisticated brain function-related techniques, abnormalities may be detected. While many mTBIs tend to result in a recovery period of days or weeks, this is not the case for all mTBIs. In attempting to draw together the neuroimaging literature in mTBI, methodological heterogeneity within these studies, particularly pertaining to imaging data acquisition, is a source of challenge to coherence in interpreting the neuroimaging data across studies [131, 132].

Mu, Catenaccio, and Lipton [131] conducted a comprehensive review of various neuroimaging techniques (structural MRI, functional MRI [fMRI], diffusion tensor imaging [DTI], fluorodeoxyglucose positron emission tomography, electroencephalography, and magnetoencephalography) investigating blast injury. The authors found that four of the five structural MRI studies reported decreased cortical thickness and decreased thalamus and amygdala volume. The corpus callosum and superior longitudinal fasciculus were the neuroanatomical regions that revealed abnormality in 8 of 18 DTI studies. Resting-state fMRI studies reported a variety of functional network differences. Other functional imaging studies showed diffuse changes in activity, especially in the frontal, parietal, temporal, and cingulate regions. fMRI studies tended to examine executive function in the task-based studies and typically revealed widespread task-related activation in blast-related mTBI participants compared to control subjects [131]. In a general sense these studies do attest to both structural and functional changes after mTBI; however, a dominant and conclusive method which precisely extrapolates neural correlates has yet to emerge.

A systematic review of DTI studies in sport-related concussion [132] found 7 of 8 eligible studies had at least some type of DTI abnormality. While neuroanatomical location was inconsistent, the variance in location is unsurprising given the heterogeneity of concussion and the variability between time of injury and DTI scanning. Changes in some regions, such as the corpus callosum, internal capsule, and longitudinal fasciculus, are reported more often than others, which may further indicate that a useful approach lies in consideration of *neural connectivity* models and the vulnerability of associated structures to axonal injury in concussion. Diffuse decrease in fractional anisotropy using tract-based spatial statistics (TBSS) were demonstrated in retired aging collision sport athletes compared to non-concussed matched controls [133].

A systematic review of magnetic resonance spectroscopy (MRS) studies in sport-related concussion [134] found that 9 of 11 studies reported differences in MR spectra between concussed athletes and controls. The MRS findings suggest that metabolic disruption continues beyond the resolution of symptoms and other objective measures in some athletes.

(Neuro-) Psychological Treatment

Active psychological and neuropsychological rehabilitation addressing persistent PCS has previously had limited empirical support [135]. Controlled trials of psychosocial approaches to interventions have predominantly focused on early intervention and prophylaxis. Education and reassurance (e.g., discussing typical symptoms, expected recovery time, and making graded increases in activity), offered either directly by clinicians [136] or via information leaflets [137], can reduce symptoms at 3–6 months post-injury [26, 138]. However, not all studies show a benefit for these approaches. Targeting at-risk groups, such as those with pre-injury psychiatric difficulties [139], may be warranted though.

A developing body of research indicates that various appraisals and coping responses may influence whether symptoms endure, such as symptom interpretation, recovery expectations, the "good old days" bias, and all-or-nothing coping [140–142]. Addressing these and associated vicious cycles that maintain or exacerbate symptoms using cognitive behavioral therapy (CBT) has been proposed should difficulties persist [135]; treatment may go beyond addressing comorbid anxiety and depression to focus on other processes that may contribute towards problems, such as fatigue and cognitive difficulties. Two randomized controlled trials of CBT, one with additional cognitive rehabilitation components [143] and one without [144], both indicated positive findings compared with waiting list controls. Reducing symptoms and improving quality of life may, therefore, be possible for individuals with persistent difficulties.

Summary and Conclusions

Neuropsychological functions appear to recover rapidly early post-mTBI. Neuroimaging studies largely demonstrate functional, rather than structural, changes post-mTBI; however, in some cases, especially in "complicated" mTBI, structural changes may also be present. Studies examining the association between neuropsychological status and radiographic neuroanatomic data suggest the functional changes in brain activation may resolve readily, but in those "complicated" cases, especially where structural changes are present, delayed recovery (at 3 months to a year) may be anticipated. There appears to be concordance between neurological findings and cognitive functions early after injury, but, with time, such associations dissipate. The relationship between subjective complaints and cognitive function also appears to weaken with time. Empirical support for the use of cognitive rehabilitation is sparse, but the role of psychoeducation and the treatment and modification of other psychosocial factors that may exacerbate post-mTBI symptoms has gained increasing support. It is crucial, therefore, that neuropsychological assessments of mTBI cases are undertaken not only to identify neuropsychological processing but also to identify and manage related issues,

with a careful eye toward monitoring return to activities. With a better understanding of the multiple causal variables that interplay in mTBI and PCS, patients and relatives may be given better advice to ensure that recovery is maximized.

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Management of Moderate and Severe TBI

Geoffrey Ling, Scott A. Marshall Jr, Randy S. Bell, and Rocco A. Armonda

Introduction

The spectrum of traumatic brain injury (TBI) is mild, moderate, or severe. TBI is defined as a complex pathophysiological process affecting the brain and induced by biomechanical forces [1]. Severity is based largely on the presenting Glasgow Coma Scale Score (GCS) (Table 1). Patients with *mild* TBI have an admission GCS of ≥13. This is often referred to as concussion. These patients may have experienced a brief (<30 min) loss of consciousness, and presenting complaints may include headache, confusion, and amnesia (The Management of Concussion in Sports (Summary Statement) 1997). Guidelines suggest appropriate neurological evaluation with concomitant neuroimaging with CT or MR after any concussion with loss of consciousness with treatment targeting symptoms [2, 3]. The spectrum of presentation of mild TBI is broad and its long-term sequelae are referred to as post-concussion syndrome, the discussion of which is beyond the scope of this chapter. *Moderate* TBI is defined as an admission GCS of 9–12 and is usually associated with prolonged loss of consciousness, abnormal neuroimaging, and neurological deficit [4]. Patients with moderate TBI will require hospitalization and may need neurosurgical evaluation or intervention. Patients with GCS scores of 8 or less have significant neurological injury and are classified as having *severe* TBI. Typically, these patients have abnormal neuroimaging, such as a

Table 1 Glasgow Coma Scale

Best motor response (M)	
Follows commands	6
Localizes to pain	5
Withdrawal to pain	4
Flexor posturing	3
Extensor posturing	2
No response	1
Best verbal response (V)	
Oriented, alert	5
Confused, appropriate	4
Disoriented, inappropriate	3
Incomprehensible speech	2
No response	1
Best eye opening (E)	
Opens eyes spontaneously	4
Opens eyes to voice	3
Opens eyes to pain	2
No response	1

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CT scan with skull fracture or intracranial hemorrhage (ICH) [5]. Such patients require rapid evacuation to a trauma center and admission to the intensive care unit (ICU) for immediate airway control, mechanical ventilation, neurosurgical evaluation, and intracranial pressure monitoring. These classifications have prognostic, monitoring, and treatment implications [6].

The initial goals in the management of a patient who sustains a moderate or severe TBI are to provide clinical stability, arrest any element of ongoing injury, preserve neurological function, and prevent medical complications secondary to severe trauma. The presence of a brain injury must be suspected in any case of severe trauma and followed closely using appropriate out-of-hospital treatment algorithms. Next, TBI patients should be triaged and evacuated to a trauma center or appropriate hospital environment with available specialized neurological care, such as neurosurgery and neurointensivist care. Once clinically stable, TBI patients move into a posture of early rehabilitation, initially in the acute care setting, and eventually to a brain injury rehabilitation center.

Clinical Evaluation

The clinical examination of a patient with a suspected TBI has both prognostic and management implications, especially in the early treatment of TBI. An organized team approach is essential to appropriate management. This begins in the prehospital or field setting with the first responder and continues to the trauma center or tertiary care hospital, where appropriate clinical decisions made in the acute period are essential for optimal outcome. The Guidelines for Field Management of Combat-Related Head Trauma and Advanced Trauma Life Support (ATLS) are both primary resources for military and civilian providers who treat TBI. The Brain Trauma Foundation publishes other guidelines related to head injury which are also helpful, including guidelines for the surgical management of TBI and prehospital management of TBI (available at http://braintrauma.org). After ensuring that the ABCs (airway, breathing, and circulation) are addressed, the provider should make a rapid initial neurological evaluation, especially determining the patient's GCS score (Table 1) [7, 8]. The GCS score is important for triage and is a quantifiable measure of impairment which can help guide early management sequences. This initial exam also helps prognosticate the outcome of moderate and severe TBI and penetrating TBI (pTBI) [9, 10].

Initial Emergency Department and Field Management

It is crucial that emergency management personnel evaluate and address the ABCs to optimize cerebral oxygenation and perfusion. The brain can tolerate severe hypoxia for a very limited period, and it is well established that the duration and severity of hypoxia and hypotension in this critical early period have dramatic consequences on the ultimate clinical outcome [11, 12]. Thus, the goals of early resuscitation are to ensure adequate oxygen saturation (>90%) and avoid hypotension (SBP <90 mmHg). Airway protection is needed in most moderate to severe TBI patients, and in many of these, mechanical ventilation support may also be required. Although many studies have failed to show a mortality benefit from early intubation, attention should be paid to maintaining normoxemia to mild hyperoxemia, as recent work has shown extreme hyperoxemia to be associated with an increased risk of mortality in severe TBI [13]. Attention to circulation starts with hemorrhage control followed by fluid resuscitation with isotonic crystalloid solution or blood products, depending upon the clinical setting.

The head should be kept in midline position, the head of bed elevated to 30°, and the cervical spine should be immobilized with a rigid neck collar. This will protect the cervical spine until cleared and allow for optimal venous drainage in order not to aggravate any developing intracranial hypertension, i.e., increased intracranial pressure (ICP). An occult cervical spine injury is assumed in all TBI patients with altered mental status or blunt injury above the clavicle until ruled out by radiographic imaging [8]. Spinal

injuries concomitant with TBI are not uncommon; a recent retrospective review of head injury casualties from the wars in Iraq and Afghanistan demonstrated a 16% incidence of spinal column trauma of various types [14].

Examination and Secondary Survey

The ATLS secondary survey examination includes a more detailed but rapid neurologic evaluation (Table 2). Examining the patient and detailing the extent of impairment are essential. Ideally, this can be accomplished in the emergency department in advance of sedation and/or paralysis for endotracheal intubation and other procedures. The diagnosis of TBI is made on history and physical examination with subsequent neuroimaging providing helpful supportive information of hypothesis testing and guiding further medical and surgical management. In evaluating a trauma patient, it is also important to remember that altered mental status or obtundation due to other causes, including impaired ventilation, oxygenation, hypoperfusion, glycemic derangement, or toxin exposure may be complicating the examination in addition to occult or obvious head injury. These conditions must be considered during the initial evaluation [8].

Neuroimaging and Vasospasm

Advanced neuroimaging is needed for the complete evaluation of moderate and severe TBI patients. Acutely, CT imaging of the brain will

Table 2 Focused neurologic exam in TBI

Specific tests	Examination pearls
Mental status evaluation testing Orientation, language evaluation, and overall level of consciousness	May be accessed quickly or indirectly while attending to other injuries
Cranial nerves (CNs) CN I: olfaction CN II: vision CN III, IV, VI: vertical and horizontal eye movements and identification of specific CN impairment, if any CN V, VII: corneal reflex and facial symmetry to painful stimuli (grimace) CN VIII: evaluation of hearing loss and rapid assessment of integrity of tympanic membrane (TM) CN IX, X: gag or cough (if intubated) response CN XI: sternocleidomastoid (SCM) or trapezius movement CN XII: tongue protrusion	CNs should be documented in every TBI patient CN I: not usually assessed unless mild TBI CN II: pupil reactivity and presence of blink to threat (BTT) or field cut on confrontational testing CN III, IV, VI: CN III and VI deficits often associated with increased ICP or transtentorial herniation events; may test with oculocephalics *only if c-spine is cleared* CN V, VII: corneal reflex testing more sensitive for subtle reactivity with cotton wisp than with saline drops CN VIII: gross testing and inspection indicated; always inspect TM prior to external canal irrigation with cold water for caloric testing CN IX, X: commonly tested with in-line suction via the endotracheal tube CN XI: ensure that C-spine is cleared prior to SCM testing CN XII: important midline command which, along with forced eye closure, may be the only command followed during emergence from coma
Motor evaluation of spontaneous movements, movements to pain, or strength on commanded movements in a cooperative patient	When administering pain for a motor response, give a stimulus in an area where a withdrawal, localization, or flexion response will be distinct movements from each other (i.e., the axilla or the inner thigh)
Sensory testing with pain sensation and temperature, vibration, and position sense in cooperative patients	Pinprick sensation in the neck, arms, trunk, and legs with evaluation of perception of via grimace or localization in the stuporous patient
Deep tendon reflexes (DTRs) in the arms, legs, and Babinski (extensor plantar) responses	DTRs provide an objective exam finding which can help confirm the presence of a lateralizing exam in an uncooperative patient
The cerebellar exam in the cooperative patient is done by evaluation of simple dysmetria of the arms and legs with finger-nose-finger and heel-shin testing	Difficult to accurately assess in the comatose, moribund, or uncooperative patient

generally provide sufficient information for the initial clinical management, with MRI offering finer delineation of traumatized neuroanatomy. Brain MRI can be quite helpful during the evaluation of TBI, but should not be used in the imaging of acute pTBI from metallic projectiles due to the risk of heat and movement of retained foreign bodies by the MRI's high magnetic field [9]. MRI should also not be used outside of the setting of overall clinical hemodynamic and airway stability. If a vascular injury is suspected, then catheter cerebral angiography is recommended. The incidence of vasospasm in the setting of blast-related pTBI is high, approaching 50% [15]. Thus, it is recommended that patients with acute pTBI from explosives undergo regular noninvasive vascular assessment via transcranial Doppler or invasive angiography for definitive diagnosis and potentially for interventional revascularization procedures [15].

Herniation Syndromes

Patients with severe TBI who develop intracranial hypertension may progress to a cerebral herniation event. Awareness of the clinical manifestations of increased intracranial pressure is paramount to managing the patient with TBI. The skull is a fixed and rigid container almost completely filled with blood, brain, and cerebrospinal fluid (CSF). Any increase in volume from hemorrhage or edema is initially compensated by displacement of blood or CSF. Herniation occurs when these compensatory mechanisms are exceeded, which manifests clinically in a variety of neurologic syndromes.

Subfalcine Herniation

Subfalcine herniation is lateral shift of one frontal lobe into the contralateral side. It can occur with any degree of midline shift (MLS). The most common clinical manifestations are increasing lethargy and, occasionally, neurological deficits related to compromised flow to one or both anterior cerebral arteries (ACAs). Unilateral ACA compromise classically causes weakness of the contralateral lower extremity, although involvement of the proximal arm and shoulder has been reported [16].

Uncal Herniation

Uncal, or lateral transtentorial, herniation occurs when a supratentorial mass pushes the mesial temporal lobe and uncus anteriorly and downward through the tentorial opening between the ipsilateral aspect of the midbrain and the tentorium. The Kernohan's notch phenomenon, with hemiparesis ipsilateral to the side of the supratentorial lesion, is a potentially false localizing sign which may present after uncal herniation [16]. Classically, a unilaterally large pupil and subsequent third nerve palsy may signal this phenomenon. Radiographic findings of uncal herniation may be seen (Fig. 1a) with resulting midbrain Duret hemorrhages (Fig. 1b, c) and midbrain ischemia (Fig. 1d) secondary to compromised blood flow to paramedian midbrain perforator vessels [16]. Although significant, patients can still have a good neurological outcome with Duret hemorrhages [5].

Central Herniation

Central herniation is downward movement of the brainstem by pressure from the supratentorial brain components. Early findings with central herniation include cranial nerve (CN) VI palsy manifesting as lateral gaze deficits, which can be unilateral or bilateral. Like uncal herniation, if this progresses, the clinical trial of a CN III palsy (including an ipsilateral nonreactive dilated pupil), coma, and posturing can occur. Posterior cerebral artery (PCA) infarctions can occur with ongoing central or uncal herniation due to compression of the PCA as it passes upward over the tentorial notch [17]. These can be unilateral or bilateral.

Extracranial Herniation

Extracranial herniation occurs when brain tissue breeches through a skull defect. Most commonly, this occurs after craniectomy as the brain can shift through the surgical site (Fig. 2) or can result from severe trauma. Extracranial herniation can occur in over 20% of postsurgical TBI patients and essentially represents therapeutic decompression of intracranial hypertension.

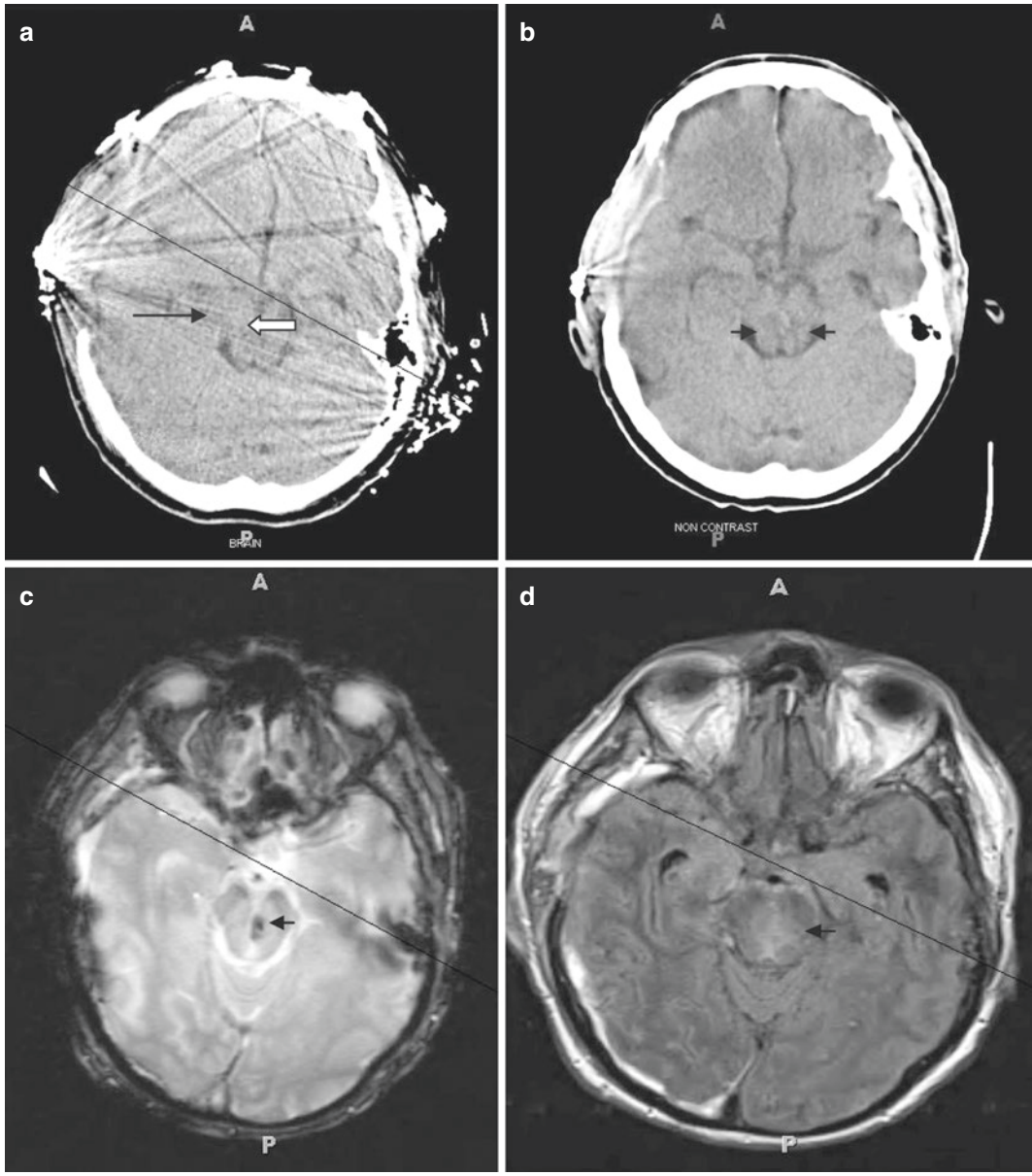

Fig. 1 (**a**) Uncal herniation: Note the lateral displacement of the uncus (*black arrow*) and compression of midbrain structures (*white arrow*). (**b**) Duret hemorrhages of the midbrain tegmentum (*arrows*) on HCT of the same patient days later. (**c**) Duret hemorrhages (*arrow*) in same location seen on GRE sequence MRI. (**d**) Duret hemorrhages and ischemic change on FLAIR MRI of the central midbrain (*arrow*)

Unfortunately, complications of extracranial herniation can manifest to include venous infarctions and cerebral cortex lacerations. Some have reported that large, rather than small, craniectomies may help to minimize complications from extracranial herniation [18].

Paradoxical Herniation

A less reported type of herniation phenomenon is paradoxical herniation, which has occurred during lumbar cistern drainage in the setting of a craniectomy. Counterintuitively, paradoxical herniation manifests by downward movement of

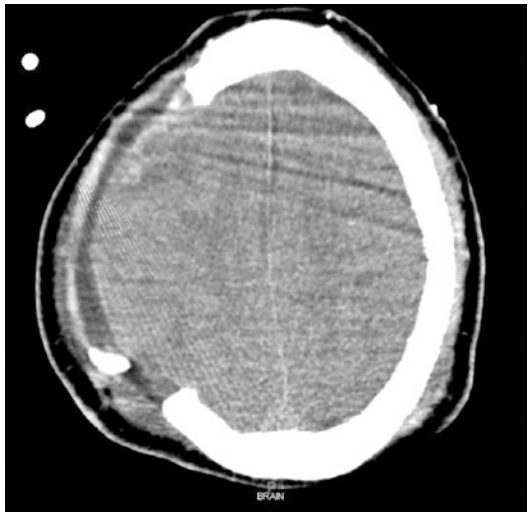

Fig. 2 Extracranial herniation through craniectomy defect

brain in the setting of an overall *lowered* intracerebral pressure (ICP) [19]. Only a handful of cases are reported, although this can likely occur in the setting of sodium dysregulation and hypernatremia. Remote cerebellar hemorrhages may be seen with paradoxical herniation. If the herniation event was precipitated by lumbar puncture, some have reported that an emergent blood patch provided reversal of the herniation syndrome [20].

Tonsillar Herniation

Tonsillar herniation occurs from displacement downward of the cerebellar tonsils into the foramen magnum and compression of the medulla. This can manifest as sudden death from apnea or hemodynamic changes due to compression of medullary respiratory and homeostatic centers. Posterior fossa hematomas with CSF outflow obstruction from the fourth ventricle may result in an acute hydrocephalus [17]. A posterior fossa hematoma or fourth ventricular dilation, distortion, or obliteration requires urgent neurosurgical evaluation for possible intervention to include suboccipital craniectomy [21].

Upward Herniation

Upward herniation is movement of brain cephalad through the tentorium into the cranium resulting in brainstem compression. Typically, this occurs with excessive or overzealous therapeutic CSF drainage from an extraventricular drain. The clinical presentation of upward herniation is not well described, although a decrease in a patient's level of consciousness progressing to an obtunded, apneic patient can be expected.

Definitive Management of TBI

Criteria for Intensive Care Unit Admission

After initial emergency care, patients with moderate and severe TBI require close neurological and physiological monitoring. This is best done in the ICU, where monitors and advanced clinical practice nurses are present. Improved outcomes are demonstrated when specialized neurological intensive care teams guide management by employing evidence-based care [22]. If present, other traumatic injuries may require management from colleagues in trauma surgery, and orthopedic, craniofacial, and other specialists, and this can be facilitated by a team approach in the neurologic ICU.

In this critical injury period, the best measure of efficacy of treatment or worsening of condition is the neurologic examination. Thus, regular clinical evaluation by skilled practitioners comfortable with neurological examination skills is needed. In the acute period, it may be as often as every hour and then less frequently if the patient remains stable. ICP and cerebral perfusion pressure (CPP) measurements should be made continuously if an ICP monitor is indicated. However, even in the presence of ICP monitoring, the importance of the clinical examination and neurological assessment cannot be overstated. The period with the highest risk for deterioration is in the first few days after TBI, which can be due to a number of factors, including concomitant critical illness. A common cause is the conversion to traumatic intracerebral hemorrhage (tICH) from a non-hemorrhagic contusional injury. This is reported to occur within the first 9 h after injury, with the peak period of cerebral edema occurring from 48 to 96 h after TBI [23]. Thereafter, it wanes, and there is clinical improvement with

better ICP control [24]. A more liberal examination paradigm by critical care staff may be reasonable to adopt after this period.

Use of Published Clinical Guidelines

As stated above, the overriding concept of management of the moderate and severe TBI patient is the prevention of secondary injury. In the initial hours after the inciting trauma, this involves mitigating elevations in ICP, tICH, cerebral edema, and hypoxia or other metabolic derangements. Treatment guidelines for the management of severe TBI published by the Brain Trauma Foundation have been instrumental in improving care through guiding therapy with evidence-based recommendations [11]. Guidelines are also available for the prehospital management of severe TBI, field management of combat-related head trauma, and surgical management of traumatic brain injury, and all four sets of guidelines can be obtained online from the Brain Trauma Foundation [25] (http://braintrauma.org).

Ventilation and Airway Management

Ensuring adequate oxygenation and appropriate ventilation of the head-injured patient is vital. Oxygenation and ventilation goals should be to maintain adequate oxygenation with the partial pressure of oxygen in arterial blood (PaO_2) remaining above 60 mmHg, and avoidance of either hypocarbia or hypercarbia by maintaining a partial pressure of carbon dioxide in the blood (PCO_2) in the 30–39 mmHg range [11, 26]. Avoidance of hypoxemia or extreme hyperoxemia ($PaO_2 > 487$ mmHg) is crucial [13]. In the field, oxygen saturation should be ≥90%. Hypoxic episodes with saturations lower than this are associated with worse outcome [27]. Absolute indication for inserting an artificial airway is a GCS score of 8 or less or suspicion that the patient's ability to ventilate or protect his or her airway is compromised. Oral endotracheal intubation is preferred. Nasotracheal intubation is not advocated in the setting of any significant head trauma as there is significant potential for increasing ICP due to nares stimulation as well as occult skull fracture, which may be worsened by nasopharyngeal manipulation [28]. A clinician may control PCO_2 in intubated patient. As increased ICP is correlated with hypercapnea, likewise clinicians should be aware that overaggressive hyperventilation should be avoided due to the potential for decreased cerebral perfusion and even ischemia at $PCO_2 \leq 25$ mmHg [11]. It may represent a better goal to avoid even approaching this level of PCO_2 for more than a very short period of time. Newer ventilator management strategies, such as airway pressure release ventilation (APRV), aimed at improving oxygenation at the expense of ventilation, require further study for use in the setting of head injury and must be used with caution due to the possibility of hypercapnea. It is suggested to monitor capnography in patients ventilated on rescue modes of ventilation with known head injury.

Management

The objective of hemodynamic therapy in TBI is to ensure adequate brain perfusion. The specific treatment goals are systolic blood pressure (SBP) ≥90 mmHg, CPP ≥ 60 mmHg, and euvolemia [11]. CPP represents the mean arterial pressure (MAP) minus ICP. Although CPP is neither a direct measure of cerebral blood flow nor of regional cerebral flow, it is indicative of the overall adequacy of global brain perfusion, especially in the context of high ICP.

Blood pressure management may be challenging in head-injured patients. Often, the patient is in hemorrhagic shock due to polytrauma injuries which accompany the head injury. Hypotension is common and is independently associated with poor outcome and mortality from TBI [29–31]. An SBP < 90 mmHg has an especially deleterious effect. When compared to hypoxia, low SBP is associated relatively with an even worse outcome [32]. With head injury, the ability of the neurovasculature to autoregulate is impaired, and, thus, regional cerebral blood flow becomes directly dependent on systemic blood pressure [28].

Experimental models show that the injured brain is highly susceptible to even subtle ischemic states [33]. It is, therefore, imperative to avoid even short episodes of hypotension after TBI.

Hemostasis of the obvious soft tissue head wound can be obtained with traditional prehospital dressings. Crystalloid fluids are used for fluid resuscitation in the field phase of TBI and polytrauma treatment. Later, blood products may be transfused as needed. From the wars in Afghanistan and Iraq, it has been reported that hemorrhagic shock is best treated with red blood cells and plasma using a 1:1 ratio based on volume [34, 35]. Colloid and hypotonic fluids are relatively contraindicated in TBI due to the fact that colloid fluids containing albumin have been shown to increase the risk of mortality when given in the setting of brain trauma [36]. Hypotonic fluids, such as 1/2 normal saline (NS) and lactated ringer's, have the potential of exacerbating cerebral edema and should be avoided [28]. Overall fluid balance of head-injured patients is also important. TBI patients who were fluid balance negative by approximately 600 cm^3 had worse proximal outcomes in a recent study [37].

CPP goals are initially met with intravenous fluids, but if adequate MAPs cannot be maintained with intravenous fluids alone, vasoactive pharmacologic agents may be considered. Norepinephrine and phenylephrine are preferred as they have the least effect on cerebral vasomotor tone. If vasopressors are being used, then continuous hemodynamic monitoring is needed with both a central venous pressure catheter and a peripheral arterial pressure catheter [24]. Aggressive use of vasopressor agents has been associated with increased incidence of acute respiratory distress syndrome (ARDS); however, this complication potentially could have been the result of exceeding CPP levels of 70 mmHg [6].

Intracerebral Pressure Management

The management of ICP is paramount in neurocritical and neurosurgical care. If ICP progresses unchecked, it will culminate in cerebral herniation, discussed earlier in this chapter. Conservative measures should be instituted in every moderate to severe TBI patient so as to minimize increasing ICP. Such simple interventions include raising the head of the bed to 30°, keeping the head midline, avoiding any circumferential neck dressings for wound hemostasis or securing the endotracheal tube, and avoiding placement of internal jugular (IJ) central venous lines into the dominant IJ. All of these will optimize venous outflow from the head. The Trendelenburg position should not be used for central access and line insertion for treatment of an acute exacerbation of increased ICP, as placing the patient into this position may serve to increase ICP further [38]. In this setting, emergency line placement should not include central lines that require Trendelenburg positioning.

Goals for ICP Treatment

The goal of ICP for the brain-injured patient is to maintain normal intracranial pressure. This is generally less than 20 cmH_2O or 15 mmHg. However, there are data to suggest that elevations over 25 mmHg are associated with poor outcome, and, thus, interventions should be aimed at reducing ICP to less than this amount. Current guidelines recommend instituting measures to control ICP when pressures of 20 mmHg are reached, and aggressive means employed to prevent ICP elevations over 25 mmHg [11]. One must keep in mind the achievable CPP based on MAP and ICP during therapy, as many interventions to decrease ICP may also have systemic effects on peripheral hemodynamics. The maintenance of a CPP of at least 60 mmHg is strongly recommended [11]. This is often accomplished with the use of vasopressor agents, although complications including higher incidence of ARDS may result from overshooting the goal CPP to greater than 70 mmHg with vasopressors and intravenous fluids, as discussed earlier in this chapter [6].

Indications for ICP Monitoring

All severe TBI patients with a strong suspicion of increased ICP should have an ICP monitor placed. There are a number of options that

include intraventricular catheter (IVC), also known as an extraventricular drain (EVD), intraparenchymal fiber-optic monitor, subdural bolt, and epidural fiber-optic catheters. The most invasive is the EVD. It provides the most accurate measurement of ICP as it is placed into the third ventricle which is almost at the center of the cranial vault. It is also the most consistently reliable, and it can be zeroed after insertion. The other methods are less invasive as they either require only minimal or no penetration of brain parenchyma. As closed systems, they have a lower incidence of infection but, unfortunately, also are subject to measurement drift as they cannot be zeroed externally once placed. Another benefit of the EVD is that it provides a treatment option for ICP management. Thus, the IVC is best referred to as an EVD, as it can be used for CSF removal, and this avoids confusion with nomenclature [11]. If hydrocephalus is seen on CT, an EVD is the best option.

Clear indications exist for placing an ICP monitor. If the patient has a GCS ≤ 8 (after resuscitation) and an acute abnormality on CT, such as tICH, compression of the basal cisterns, and evidence of contusion or herniation, then an ICP monitor should be placed [11]. If a patient has two of the following—SBP ≤ 90 mmHg, motor posturing on exam, and/or age ≥ 40 years—then an ICP monitor should likewise be placed or strongly considered [11]. Typically, a neurosurgeon places these devices. However, there is evidence that with proper training, placement of an EVD or other ICP monitors can be done safely by neurointensivists [39, 40]. It should be stated that this is not yet a mainstream practice and that access to the cranial vault should be obtained only with close neurosurgical oversight and advanced training in these procedures. Other monitoring devices, such as brain tissue oxygenation monitors, microdialysis catheters, and jugular venous saturation monitors, can be used to tailor therapy, but widespread or routine application of these devices is not recommended at this time pending further study of variables which may be manipulated and subsequent outcome with the help of the information these monitors provide [11].

Medical Treatment Options for ICP Management

Initial medical intervention for elevated ICP usually includes avoidance of exacerbating factors, such as fever, seizures, hyperglycemia, or hypercarbia. The next line of therapy involves pharmacologic creation of an osmotic gradient causing movement of water from intracellular and extracellular compartments of the brain into the vasculature, where it reduces the volume of the overall cranial compartment [38]. Several agents have been used for this purpose in the past, but currently mannitol and hypertonic saline (HTS) are the mainstays of hyperosmolar therapy.

Mannitol

Mannitol should be given intravenously via a peripheral or central intravenous line at a dose of 0.25–1.0 g/kg. Small doses of mannitol (0.25 g/kg) have been shown to effectively reduce ICP in patients with TBI [41]. Earlier data show that mannitol use in TBI correlates with decreased ICP and improvements in cerebral blood flow and CPP [42]. Past recommendations for mannitol to be given as bolus infusions rather than continuous are no longer supported. Still, in common clinical practice, a single bolus dose is most widely used [11]. So long as serum osmolality is followed closely, additional doses of mannitol can be given. A serum osmolality of 320 mOsm/L is generally accepted as the treatment end point, although some investigators advocate that slightly higher levels can be obtained with caution [43].

Hypertonic Saline

Another option for hyperosmolar therapy is HTS. Studies using 7.5 and 23.4% HTS provide evidence of efficacy. Recent evidence supports the use of bolus doses of 30–60 ml of 23.4% HTS to emergently reverse a herniation event [44]. An additional benefit of using 23.4% HTS is that its ameliorative effect on ICP lasts longer than that of mannitol [45]. When used, 23.4% HTS must be administered via a central venous line over 10–15 min to prevent phlebitis and hypotension. A commonly used initial treatment goal is to achieve serum sodium levels 145–155 mEq/L,

which is equivalent to a serum osmolality of 300–320 mOsm/L in most patients [38]. Recent evidence shows 23.4% HTS to be effective in reducing ICP by a mean value of 8.3 mmHg when given for ICP >20 mmHg and can increase CPP values by 6 mmHg when pre-treatment values are <70 mmHg [46]. A continuous intravenous infusion of 2 or 3% HTS can be used to maintain high serum osmolality and does not have the issues of causing systemic hypotension as do higher concentrations of saline. When using 2 or 3% saline, it is suggested that the fluid be made as a 50:50 mix of sodium chloride and sodium acetate so as to prevent hyperchloremic metabolic acidosis. At a 2% concentration, HTS can be given through a peripheral intravenous catheter, but at 3% or higher, it should be given via a central line due to its potential to cause phlebitis. Other published recommendations have suggested that 3% saline can be safely administered peripherally or via intraosseous access [47]. Infusion rate is set based on the particular patient's intravascular needs. Typically, a maintenance rate of 75 cc/h is used. However, these solutions can be administered in 250 cc boluses to treat episodes of intracranial hypertension or as a volume expander to treat systemic hypotension.

If continuous infusions of hypertonic saline are used, serum sodium should be monitored every 6 h or more frequently. Rapid drops in serum sodium are to be avoided so as not to precipitate cerebral edema [48]. Care must be taken when increasing serum sodium levels from hyponatremic states to avoid central pontine myelinolysis (CPM). Dehydration must likewise be avoided [37]. Generally, HTS therapy is maintained for the first 4–7 days after injury, and after the peak edema period elapses, HTS infusions can be switched to normal saline or terminated while observing the serum sodium level for the slow return to normonatremia.

Other Pharmacologic Agents to Reduce ICP

If ICP remains poorly controlled after the efforts described above, then induced pharmacologic coma can be considered. The postulated effect of pharmacologic coma on ICP is through reduction of cerebral metabolism, measured by the cerebral metabolic rate of oxygen ($CMRO_2$) with concomitant reductions in cerebral blood flow and reduced tissue oxygen demand. The most commonly used agent for pharmacological coma is pentobarbital. This drug can be administered intravenously at a loading dose of 5 mg/kg, followed by an infusion of 1–3 mg/kg/h. There is a higher-dose regimen that begins with an intravenous loading dose of 10 mg/kg over 30 min followed by 5 mg/kg/h infusion for 3 h, followed by 1 mg/kg/h titrated to therapeutic goals, which are either burst suppression on continuous electroencephalography (EEG) monitoring or a reduction in ICP [24]. If burst suppression is not obtained with this dose, then a smaller loading dose and increased rate can be given until a satisfactory EEG tracing is seen or ICP is controlled. Recall that additional loading doses must be part of any increase in barbiturate therapy, as only increasing the continuous infusion rate will not affect ICP, EEG, or serum levels for some time. Other barbiturates may be used, including the much shorter acting thiopental, whose half-life of 5 h is suited for short-term therapy of elevations in ICP [38]. Thiopental doses of 200–500 mg can be given via bolus intravenous push while monitoring for hypotension. Use of this medication is reserved for patients with a definitive airway.

Another option for pharmacological coma is propofol, which is given at an intravenous loading dose of 2 mg/kg, followed by a titrated infusion of up to 100 mcg/kg/min. The use of propofol for this clinical indication is controversial. In terms of efficacy, a study using propofol for ICP reduction showed a failure of an improvement in 6-month outcome benefit [49]. Long-term and high-dose propofol infusions have been associated with the development of propofol infusion syndrome, which consists of renal failure, rhabdomyolysis, hyperkalemia, myocardial failure, metabolic acidosis, lipemia, hepatomegaly, and death. The mechanism for this is not fully understood, but significant caution must be used in any infusion over 5 mg/kg/h or treatment lasting longer than 48 h [11]. If propofol is to be used, then similar to pentobarbital therapy, continuous EEG monitoring is helpful as the therapeutic goal will be burst suppression and/or ICP control.

Hyperventilation and Induced Hypothermia

Hyperventilation for ICP reduction may also be considered, but only as an emergency, temporary intervention. Prolonged hyperventilation has been clearly associated with exacerbation of cerebral ischemia [50]. Short durations of hyperventilation are acceptable as a temporizing measure until other (surgical, hyperosmolar, metabolic) means of managing increased ICP are available. If hyperventilation is continued for longer than 12 h, metabolic compensation negates the ameliorative effects of respiratory alkalosis caused by a hypocapnic state and continued hyperventilation may be harmful. The recommended goal for a chronic PCO_2 is 35–40 mmHg, but during an impending herniation event, hyperventilation will acutely lower PCO_2, as well as ICP, within seconds. The current recommended PCO_2 is to strictly avoid levels below 25 mmHg [11, 28].

Induced hypothermia for TBI remains controversial but promising. Recent animal data show promise for induced hypothermia with improved neurophysiologic metrics in an asphyxial brain injury model [51]. There is also data in brain trauma that induced mild hypothermia (33–35°) may improve outcomes as far out as 2 years post-head injury [52]. Current use of prophylactic hypothermia for treatment of ICP in severe TBI is a second-tier therapy but may be helpful in refractory intracranial hypertension. If utilized, modalities of induction of hypothermia include skin-applied gel cooling systems and intravenous methods, as well as traditional air-circulating cooling blankets, iced gastric lavage, and surface ice packing [38]. Unlike induced hypothermia, the goal of maintaining normothermia and avoiding hyperthermia in TBI patients, however, remains strongly recommended [53]. The potential coagulopathic and antiplatelet effects of hypothermia should be considered, especially in the setting of hemorrhagic TBI [54–58].

The Brain Code

When ICP elevation becomes an emergency or is persistently outside of established goals, an important change in the neurological exam is manifest, or a herniation event occurs, a brain code should be performed. This term has gained popularity and many feel that a codified approach to a herniation event or other acute elevation in ICP is best managed via a treatment algorithm, similar to an advanced cardiovascular life support (ACLS) protocol. This may encourage non-neurologist or non-neurosurgeon ICU practitioners to develop a standardized approach to such emergencies [59]. An example of one such algorithmic approach to the management of elevated ICP is presented in Fig. 3.

Clinical Approach for Treating Elevated ICP

An approach that may be followed involves initial treatment of elevations in ICP with confirmation that the waveform and ICP reading is accurate. Seizure activity must be ruled out if suspected. Brain CT imaging should be considered in any new manifestation of increased ICP without explanation. Maneuvers, such as repositioning the head to midline using the head of bed to 30°, establishing normothermia, and cessation of suctioning or other noxious stimuli, may help lower temporary spikes in ICP. If this is unsuccessful, and the ICP is felt to be accurate, a brief period of hyperventilation of intubated patients may be performed. If central access exists, then 30 cm^3 of 23.4% HTS may be given via a central line over 10–15 min. Alternatively, mannitol may be given via a peripheral line. The dose of mannitol chosen depends on the clinical situation. If a herniation event has manifested, then 1 g/kg is given. If a less severe clinical situation exists, then lower doses such as 0.25–0.5 g/kg may be used. In a herniation event, central access should be readied, likely with the placement of a femoral central venous catheter to avoid the placement of the patient in Trendelenburg position to gain jugular vein access, which may elevate ICP [38]. It is reasonable in any patient with moderate or severe TBI and concerns for elevated ICP to have central venous access placed early, either in the subclavian or femoral veins.

If ICP continues to be elevated after these maneuvers, then additional HTS can be given as well as further boluses of mannitol, treating up to a serum osmolality of approximately

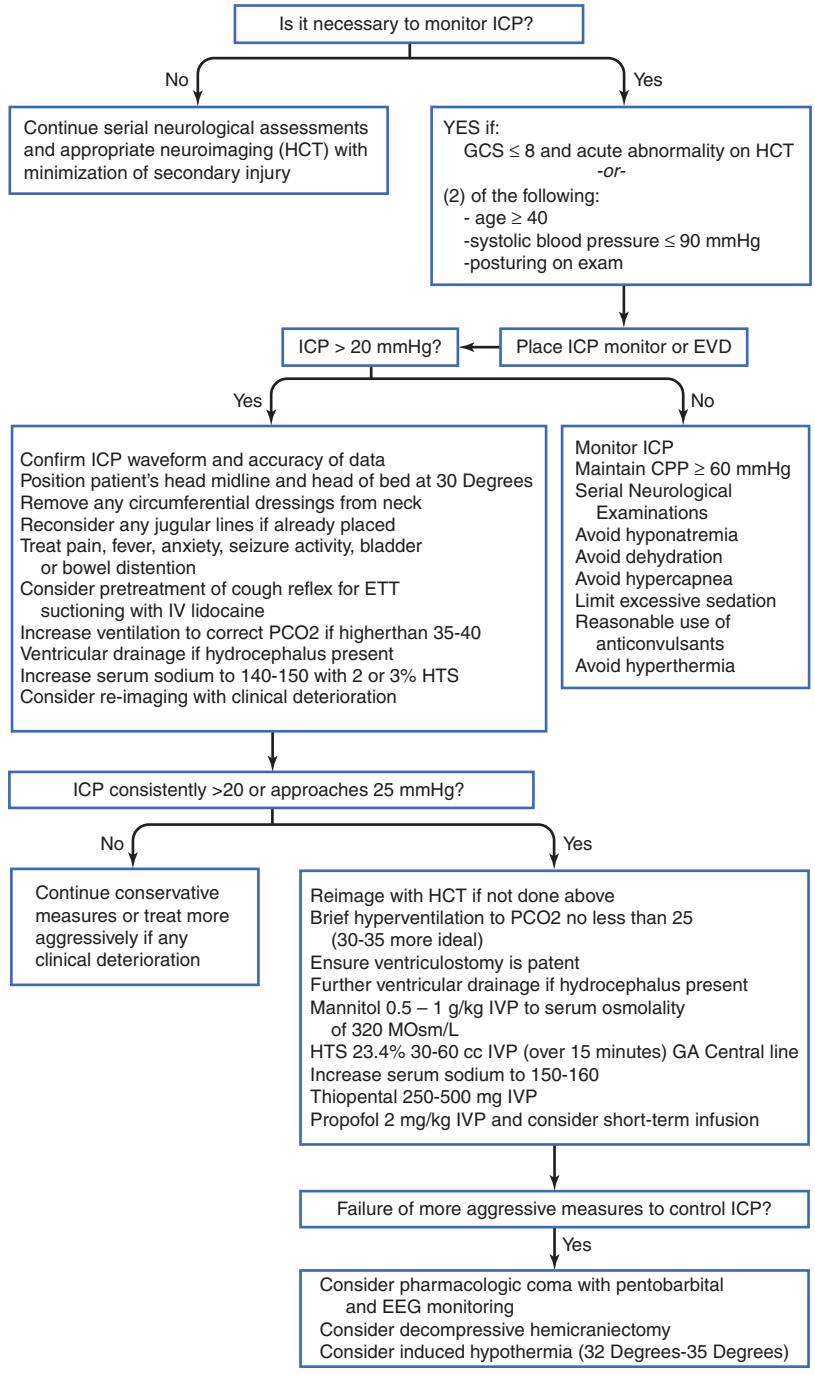

Fig. 3 An example of a brain code algorithm

320 mOsm/L. Standing infusions of HTS such as 3% can be started or increased, with goal sodium values that may exceed 160 mEq/L. Further medical management includes use of bolus doses of propofol and thiopental and consideration given to pharmacologic coma, induced hypothermia, or surgical intervention as discussed in the next section.

Surgical Treatment Options

Extraventicular Drains

As discussed above, if acute hydrocephalus, with or without obstructive hydrocephalus, is complicating the clinical picture, then the placement of an EVD may be indicated. Guideline-based recommendations detailed earlier in this chapter give indications for ICP monitoring, and also the choice of the monitor is influenced by the need for therapeutic intervention with direct CSF drainage [11]. If there is any concern for increasing or clinically relevant hydrocephalus on imaging, an EVD should be considered as the initial surgical option for treating increased ICP.

Craniectomy

Decompressive craniectomy (DC) is a controversial clinical approach to the early intervention and management of TBI. Recently, 2 clinical trials of DC were completed. They are the decompressive craniectomy in diffuse TBI (DECRA) and randomized evaluation of surgery with craniectomy for uncontrollable elevation of intracranial pressure (RESCUEicp) [60, 61]. The DECRA trial, for which DC was a Stage 2 treatment option for uncontrolled increased ICP, did not show benefit. The RESCUEicp trial was a Stage 3 ICP therapy, i.e., after medical therapy failed, and, importantly, also included patients who underwent craniotomy for removal of hematoma. RESCUEicp showed benefit in survival and ICP control but at the cost of increased persistent vegetative state outcomes. For the moderate to good recovery level, DC was not better than medical therapy alone [62].

The US military neurosurgical experience in Operation Enduring Freedom and Operation Iraqi Freedom supports early hemicraniectomy for treating some cases of severe TBI with concerns for imminent elevations in ICP, whether from penetrating, blunt injury, or blast-induced [63]. In a comparison of GCS of patients at the time of head trauma and at discharge, TBI patients who underwent a craniectomy had a lower initial GCS than those who underwent craniotomy, but at discharge their GCS was not significantly different. This implies that although these patients were worse initially, they improved after DC to the point where they appeared indistinguishable from those who initially presented with a better neurologic exam [15]. A more recent study has shown similar findings, with mean follow-up outcome of 11 months ascertained by use of the Extended Glasgow Outcome Scale (GOSE) [64]. In this retrospective review, 12 of the 18 survivors of severe TBI treated with DC had a favorable outcome.

One distinguishing difference between the DC performed in the war theaters and that of the DECRA and RESCUEicp trials is the time to surgery. In the military, DC was performed very quickly after injury. In military clinical practice, the goal of initial surgery is to stabilize the patient for a long (typically 16–20 h evacuation times) transport out of the war theater. The medical and nursing attendants on military medical transport planes are expert in critical care but have limited resources. DC is performed to prophylactically reduce the risk of increased ICP. Thus, DC is performed within a few hours of injury as opposed to >24 h for DECRA and >12 h for RESCUEicp. This earlier use of DC may be an important factor in why military DC patients seem to have better outcomes. Further study of DC is indicated.

Other Considerations

Anticonvulsants

TBI patients are at risk for both early (less than 7 days) and late (more than 7 days) post-traumatic seizures. This risk is worsened by tICH. A seizure in the acute phase can exacerbate the injury. Phenytoin, a well-established antiepileptic drug (AED), has been shown to be beneficial in reducing the risk of seizures during the first week after TBI [65, 66]. Carbamazepine, phenobarbital, and valproate are also effective AEDs [66]. Unfortunately, no AED has been shown to prevent the development of late post-traumatic seizures. Studies have shown that when followed for 15 years after TBI, approximately 50% of patients

will develop late seizures. As 50% will not, the recommended approach is to stop AED therapy after the first 7 days and only reinstitute treatment should late seizures manifest [11]. Additionally, the potential for cognitive and other side effects of phenytoin in other types of vascular neuropathology makes prolonged prophylactic use of this medication less attractive [67]. If a patient requires intravenous medications, alternatives to phenytoin and fosphenytoin are valproate and levetiracetam. Intravenous lacosamide is now available, but, to date, reports have not been published for its use in the setting of TBI [68]. Levetiracetam has not undergone a rigorous human clinical TBI trial but has been shown to be highly effective in preclinical TBI models and limited human study [48, 69, 70].

There is little evidence to support or refute the use of AEDs for prevention of post-pTBI seizures. The risk of seizure following pTBI is much higher than nonpenetrating TBI, and thus AEDs are prescribed by most providers. The guideline recommendation is to use AEDs during the first 7 days after pTBI and then discontinue. Should the patient suffer a late seizure, the AED therapy can be restarted. Therapeutic options are phenytoin, fosphenytoin, carbamazepine, valproate, or phenobarbital [9]. Currently in clinical practice, levetiracetam is commonly used in this setting.

Venous Thromboembolism Prophylaxis

Other important considerations include prevention of secondary complications of critical illness, including venous thromboembolism (VTE), gastric stress ulcers, and decubitus ulcers. Immobilized patients are at high risk for developing deep venous thrombosis (DVT) with subsequent VTE. The optimal approach for VTE/DVT prophylaxis in severe TBI complicated by ICH is uncertain. Sequential compression devices (SCDs) on the lower extremities are minimally invasive and are not associated with worsening intracranial hemorrhage. Thus, they should be placed as soon as possible if no contraindications exist, such as known DVT or loss of skin integrity from burns or trauma. The optimal timing of introduction of unfractionated or low-molecular-weight heparin for VTE prophylaxis in head trauma is less clear. However, if there are no contraindications to heparin use, then treatment should be started as soon as possible, ideally within the first 36 h after injury [71]. The routine placement of inferior vena cava (IVC) filters is controversial, and placement is currently supported only by a low-level recommendation in patients with a GCS < 8 and contraindications to anticoagulation [71, 72].

Hemoglobin

When treating TBI, the optimal hemoglobin level before transfusion is indicated, i.e., transfusion trigger, is Hb <7.0 g/dL. A recent prospective intention-to-treat study of TBI patients by Robertson and colleagues tested transfusion triggers of 7.0 vs 10.0 g/dL [73]. The results showed that the lower Hb transfusion trigger had more favorable outcomes and fewer thromboembolic events.

Gastric Ulcer Prophylaxis and Skin Breakdown

Gastric stress ulcers may be prevented using either H2 antagonists or proton pump inhibitors (PPIs). Recall that the literature is currently illuminating concerns with the indiscriminate use of PPIs and the possibilities of drug–drug interactions; thus, consideration of alternative means of gastric ulcer prophylaxis should be made in the uncommon event that a patient with TBI must be maintained on an antiplatelet regimen [74]. Either one of these medications should be used for gastric stress ulceration prophylaxis in severe TBI patients, although the tendency for H2 blockers to cause thrombocytopenia may limit their usefulness [75]. Prevention of skin breakdown is a concern in all severely injured trauma patients, and care must be taken to reduce the likelihood of decubitus ulcers through frequent repositioning, vigilant nursing care, and good skin hygiene practices.

Future Directions

The potential benefit of induced hypothermia in TBI has been discussed above, and this remains an area of great interest. Basic and clinical scientists remain optimistic and are actively engaged in research seeking new diagnostic and treatments for TBI. For diagnostics, the Brainscope Ahead 300 was recently FDA approved for TBI and intracranial hemorrhage risk assessment [76]. For treatment, glyburide, a well-known sulfonylurea oral hypoglycemic drug, when given systemically reduces edema in preclinical models of TBI, spinal cord injury, and stroke [77–79]. In a human Phase II clinical trial for stroke, Sheth and colleagues recently demonstrated that intravenously administered glyburide reduced cerebral edema and had a trend toward improved functional outcome [80]. A study in TBI is planned. Other ongoing work in moderate and severe TBI includes hyperbaric oxygen therapy, tranexamic acid, ketamine, recombinant human erythropoietin, and enhanced oxygen-carrying molecules, such as oxycyte perfluorocarbon, as neuroprotective agents or therapeutic adjuncts in the medical management of TBI [81, 82].

Summary

Medical and surgical management of the moderate and severe TBI patient is challenging. The prehospital and hospital care of TBI are largely confined to supportive efforts to minimize secondary injury for optimal neurologic recovery. This is accomplished through maintaining brain perfusion, controlling ICP, and preventing morbidity associated with critical illness. As new pharmacologic and medical approaches are introduced, there will be increasing opportunity to better manage these patients and enhance their long-term neurologic outcomes.

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Sports Concussion

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Introduction

Concussion, or mild traumatic brain injury (mTBI), is a persistent problem in athletic participation and competition. Full-contact sports, such as football, boxing, soccer, hockey, rugby, and basketball, report the highest incidence of sports concussions, but these injuries also occur in other sports and even recreational activities. An estimated 1.6 to 3.8 million sports-related concussions occur in the United States every year, and estimates reveal that as many as 50% go unreported [1, 2]. Therefore, defining, assessing, and treating these injuries have become a critical focus for physicians, coaches, and players alike. Recent evidence that repeated concussions can have long-term or even fatal effects has raised policy questions on diagnosis and return-to-play (RTP) guidelines. Increased participation in athletics at both the high school and collegiate levels has exposed more and more youths to concussion risks [3]. The increase in participation and competition also means that elite athletes are sometimes subject to the effects of multiple concussions over many years of athletic competition prior to their college or professional careers. Some neurocognitive testing has been developed to assess the damage caused by concussions and to categorize injury severity and necessary treatment. Recent discoveries of chronic traumatic encephalopathy (CTE) or abnormal (pathological) deposition of tau protein in brain tissue during brain autopsies of National Football League (NFL) players highlight that there is still much to learn.

In this chapter, we review the literature on the etiology and sequelae of sports concussions, highlight areas of interest for future research, and present a summary of the compilation of guidelines published in the literature on triage and treatment of concussive injuries in both youths and adults.

Etiology and Symptoms of Sports Concussions

The etiology of sports concussions varies from sport to sport, but common mechanisms of injury

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include rotational acceleration (shearing), linear acceleration (compressive and tensile stresses on axons), carotid artery injuries, and deceleration on impact [4, 5]. An increase in technological advances in protective gear and more aggressive play has increased the risk of catastrophic head injury associated with greater force of collisions and higher speed of play in full-contact team sports [6].

In football, the nature of the sport and the speed and frequency of player-to-player contact place the athlete at high risk for injury. One insurance company reported that the injury rates in organized high school football are double that of the general population [7]. The popularity of football across ages and regions of the United States further contributes to the public health concern, with estimates that as many as 1.5 million young men participate in American football at the high school and collegiate levels alone. An estimated 1.2 million football-related injuries are sustained annually, with concussions accounting for up to 5% of these injuries [7–10]. In the 2015 NFL season, there were 199 recorded concussions, with long snappers being the only position not to receive one and the highest instance of concussions recorded at the position of cornerback [11]. The majority of these injuries are likely sustained during direct competition; a 2-year study of over 6000 football players found that the rate of injury in games is 8.6 times higher than in practice, which is consistent with previous reports on other sports [9]. More recently, Meehan and colleagues [12] reported that approximately 78.5% of concussions occurred during game settings rather than practices in high school athletes. Dompier and colleagues found that while football practices were a major source of concussion for all three competition levels (youth, high school, and collegiate football), the rate for concussion was higher in games than in practice [13].

The risk of concussion in boxing is especially high since injury is a goal of the sport; a concussion is an objective rather than a competitive risk [14]. Boxers are subject to numerous and sometimes rapid, consecutive blows to the head, whether concussive or sub-concussive. As a result, these athletes often demonstrate a range of neurological defects [15]. A longitudinal study of 484 amateur boxers revealed statistically significant correlations between number of bouts completed before the baseline examination and changes in memory, visuospatial ability, and perceptual/motor ability 2 years later [16]. Another study of 41 boxers and 27 control subjects revealed that boxers performed worse on psychometric tests than controls and that the boxers with more bouts performed worse than the boxers with a smaller number [17]. Furthermore, boxers had more aberrations in cerebral perfusion than controls, as detected by positron emission tomography (PET) imaging. Incidence of CTE in boxers varies throughout the literature, due to differences in definitions and methods used to detect the condition. A 1969 study by Roberts [18] still holds as the best estimate of CTE in professional boxers. He sampled 244 random boxers from a pool of 16,781 retired professional boxers and found that 5% had severe CTE and 17% had lesions of the nervous system. The severity of the conditions was directly linked to the length of each boxer's career and the number of matches fought. Unfortunately, due to the nature of diagnosing CTE post-mortem, studies on the topic are retrospective and therefore unlikely to provide true incidence numbers [19].

Unlike football and boxing, soccer is not traditionally considered to be a high-risk sport. Recent studies, however, have revealed a high rate of concussive injuries among soccer players, which is particularly significant when you consider that soccer is the most popular sport in the world. Within the United States alone, there are an estimated 12.5 million [20] to 18.2 million [21] soccer players. This number dramatically increases to 265 million soccer players worldwide [22]. Covassin, Swanik, and Sachs [23] identified 22% of all soccer injuries as concussions. Comstock and colleagues [24] reported that player-to-player contact is the leading cause of soccer-related concussions, with head-to-ball contact (i.e., "heading" the ball) as the second leading cause. An overwhelming majority of these injuries are incurred during matches, rather than during training [25]. While both male and female soccer players are at a risk for suffering a concussion, multiple studies have shown that the symptoms due to

injury last longer in women than in men [26–28]; 8 days post-injury, female concussed athletes reported more total post-concussive symptoms than men, as well as scored worse on verbal and visual memory tests, after controlling for body mass index (BMI) [29]. BMI was controlled for due to the association between higher BMI and reduced cognitive function [30]. Moreover, younger female soccer players report higher concussion rates than women of older age groups, with most of the young concussed athletes continuing to remain in the game despite the presence of concussion symptoms [31]. Therefore, while all soccer players are at risk for sustaining a concussion, great attention should be paid to preventing, recognizing, and treating concussions among female athletes, specifically those of younger age. It is especially important to highlight the need to remove an athlete who is suspected of having a concussion in order to prevent further injury. The risk of brain changes secondary to playing soccer extends beyond those due to concussions alone and will be discussed further in the neuroimaging portion of this chapter [32–34].

Hockey is a popular sport in both Canada and the United States. It is estimated that for the 2008–2009 season, roughly 550,000 youths (age 9–16 years) participated in ice hockey in Canada and 340,000 in the United States [35]. Concussions are the most common specific injury occurring in ice hockey players and account for more than 15% of all injuries in youth players [36, 37]. Body checking, or deliberately getting in the way of an opponent using one's own body, is associated with 45–86% of all injuries, including concussions [36, 38, 39]. A 2010 study conducted by Emery found that in leagues that body checking is acceptable, there is three times the risk of concussion and serious concussive injuries [35]. Concussion reporting in sports is not always seen as something of high importance. A study by Kroshus [40] found that targeting the perceived concussion reporting norms may be an avenue for repairing the underreporting of concussions among hockey players. The study found that players who believed most athletes reported symptoms of a concussion were more likely to report their own symptoms [40]. Thus, concussion education and awareness is crucial to recognizing concussions and removing a player from the activity before further neurological damage occurs.

Recognition of head injury is easy when there is a loss of consciousness (LOC). The majority of sports concussions, however, occur without a LOC [41–43]. When it is difficult to make accurate sideline diagnoses, players are more likely to remain in the game or RTP too soon after injury. Internal and external pressures from players and their communities also increase the likelihood that they will not seek adequate medical attention immediately. As LOC may or may not occur with mild concussions, it is important to be aware and look out for other immediate effects of concussions including vacant stare, delayed verbal and motor responses, confusion, inability to focus attention, disorientation, slurred or incoherent speech, gross observable incoordination, disproportionate emotions, and memory deficits/post-traumatic amnesia [44]. As the brain is possibly the most variable of human organs in its response to external stimuli or insult [45], it should come as no surprise that the clinical presentation of concussed athletes varies significantly from individual to individual. In addition to individual differences, contributing factors to varied presentations include biomechanical forces involved and the athlete's prior history of injury, among others [46, 47].

Concussed individuals do commonly describe a similar set of symptoms after injury, including headaches, dizziness, confusion, disorientation, and blurred vision [48]. Balance problems are present after 30% of concussive events [48], and nausea and emesis are also common [49]. In children, symptoms typically include restlessness, lethargy, confusion, or irritability. The adult symptoms were classically thought to suggest intracranial lesions, but the data supporting these conclusions are sparse [49]. In fact, fewer than 1% of patients with minor head trauma have surgically significant lesions [50]. The consequences of a concussion can last for several days. McCrea and colleagues [51] found that concussed football players continue to show acute symptoms, such as balance problems, for at least 5 days,

Table 1 Risk factors for concussive injury

High risk	Medium risk	Low Risk
Focal neurologic findings	Initial GCS score of 15	Currently asymptomatic
Asymmetric pupils	Brief LOC	No other injuries
Skull fracture on clinical examination	Post-traumatic amnesia	No focal deficits on examination
Multiple trauma	Vomiting	Normal pupils
Serious, painful, distracting injuries	Headache	No change in consciousness
External signs of trauma above the clavicles	Intoxication	Intact orientation/memory
Initial GCS score of 14 or 15		Initial GCS score of 15
Loss of consciousness		Accurate history
Post-traumatic confusion/anemia		Trivial mechanism
Progressively worsening headache		Injury more than 24 hours ago
Vomiting		No or mild headache
Post-traumatic seizure		No vomiting
History of bleeding disorder/anticoagulation		No preexisting high-risk factors
Recent ingestion of intoxicants		
Unreliable/unknown history of injury		
Previous neurologic diagnosis		
Previous epilepsy		
Suspected child abuse		
Age older than 60 years or younger than 2 years		

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with some cognitive impairments lasting up to 7 days post-injury. Every individual suspected of having a concussive injury needs a thorough neurological examination, but the need for additional diagnostic testing, including detailed mental status examinations, depends upon the individual's risk factors (Table 1).

Lasting Effects of Sports Concussion

There is a plethora of research suggesting that sustaining a concussion increases the risk of incurring additional concussions [52, 53]. A study by Zemper [54] examining 15,304 football player-seasons at the high school and collegiate levels found that the relative risk for repeat concussions in individuals with a history of concussion is 5.8 times greater than in individuals with no prior history of concussion. In a study of 4251 player-seasons, Guskiewicz [55] also found a positive association between the reported number of previous concussions and the likelihood of incident concussion. Specifically, as compared to players with no concussive history, players who reported a history of 1, 2, or 3 or more previous concussions were 1.5, 2.8, and 3 times, respectively, more likely to have sustained a subsequent concussion.

The risk of sustaining multiple concussions is especially concerning since the long-term effects of concussions are still unknown but likely to be cumulative. Over 40 years ago, Gronwall [56] reported that the rate at which young adults process information is reduced more in those who have suffered two concussions compared to those who have suffered one concussion. More recently, research suggests that concussive effects become cumulative after 3 injuries. Collins [57] reported that athletes with three or more concussions are more likely to experience on-field LOC (6.7 times greater likelihood), anterograde amnesia (3.8 times), and confusion (4.1 times) after a subsequent concussion. Also, studies of high school and collegiate athletes using ImPACT testing (an automated neurocognitive test battery) showed that there are no detectable cumulative effects of only one or two previous concussions [58] but marked effects in athletes with three or more concussions [59]. This multitude of findings highlights the need for adequate prevention and treatment of concussive injuries.

The lasting effects of sports concussions were first highlighted in the public eye in the early 1990s when NFL players Al Toon and Merrill Hoge retired from the league because of prolonged post-concussion syndrome (PCS). Some reviews report an incidence of PCS of approximately

10–20% of concussed athletes [47]. Symptoms of the syndrome include headache, dizziness, anxiety, and impaired cognition and memory [60]. These symptoms affect more than 58% of patients 1 month after injury [61] and 15% of patients 1 year after injury [62]. PCS is characterized by lingering deficits due to the occurrence of a concussion. To be considered PCS, there must be a minimum of three symptoms present, for at least 3 months since the injury, as well as neuropsychological dysfunction [63]. The presence of headache, nausea, and dizziness during the acute head injury assessment increases the risk for subsequent development of PCS; a report of all three symptoms is associated with a 50% likelihood of PCS at 6 months post-injury, while an absence of all three symptoms reduces likelihood to 28%. The findings of lasting effects of concussive injuries and the underlying cause of PCS are still unknown. The pathophysiology of acute symptoms has been supported by animal studies demonstrating a neurochemical and metabolic cascade that detrimentally affects cognitive functions for up to 2 weeks after a concussive injury [64, 65]. Differences in development of PCS, however, point toward an additional psychopathological cause to this long-term disorder which we have yet to elucidate [63].

Alongside PCS, the discovery of the rare "second impact syndrome" (SIS) has led to considerable concern in athletes of all levels. First noted in 1984 [66], there have since been several other reports on this syndrome in the literature [67, 68]. In 2011, the death of a 22-year-old starting fullback for the Frostburg State University Bobcats was attributed to uncontrollable brain swelling that may have been caused by repeat concussions leading to SIS [69]. With SIS, athletes suffer a concussion, usually mild, and sometimes, but not always, with LOC. The athlete typically returns to play within a few days of the first hit and sometimes even within the same match as the initial injury. Cantu [70] outlined ten cases of suspected SIS, with six individuals surviving the repeated blows but incurring devastating neurological cognitive, visual, motor, and sensory deficits. Four of the reported cases resulted in death. Following the second impact, none of the athletes lost consciousness immediately, but within minutes all fell into a coma, with symptoms of blown pupils, respiratory arrest, and signs of brain herniation – all of which are typical of SIS [70]. These cases of SIS show that repeated episodes of mild brain injury occurring within a short period of time can be catastrophic and even fatal. This highlights a drastic need for proper initial diagnosis and subsequent removal from play until complete recovery, as well as increased education and improved vigilance surrounding athletes with head injuries.

One of the more severe consequences of multiple concussions an athlete may suffer over the course of a career is CTE. First described by Harrison Martland [71] in 1928 as dementia pugilistic, CTE is characterized by early symptoms of slight mental confusion, a slowing of muscular movements, hesitancy in speech, and hand tremors. In time, these symptoms become more severe and progressive, including speech and gait disturbances, pyramidal tract dysfunction, memory impairment, extrapyramidal features, behavior or personality changes (including increased aggression), and psychiatric disease [72–75]. In 1973, Corsellis [15] identified the neuropathology of this syndrome in the brains of 15 deceased boxers, 8 of whom were national or world champions. Through autopsy, he found that the neuropathology of CTE was characterized by cavum septum pellucidum, degeneration of substantia nigra, septal fenestrations, cerebellar scarring, diffuse neuronal loss, and prominent neurofibrillary tangles, now known to be composed of tau protein. In the mid-2000s, the term, "CTE," entered the public lexicon when the first documented cases of symptoms suggestive of CTE in retired NFL players were published [76, 77]. Since these initial reports, the presence of neuropathological changes associated with CTE has been confirmed at autopsy in numerous professional football players via an ongoing prospective research program entitled C.O.N.T.A.C.T (Consent to Offer Neural Tissue of Athletes with Concussive Trauma). This program was initially comprised of 150 former athletes, including 40 retired and 3 active NFL players, but has grown to include more than 196 brain tissue donations and 700 registered future donors [78]. All participants have

agreed to be interviewed annually by phone throughout their lives and, upon their death, to donate their brains for examination by the Center for the Study of Traumatic Encephalopathy (CSTE), an independent academic research center located at the Boston University School of Medicine [79]. In 2009, McKee and colleagues [80] reviewed all 47 of the neuropathologically confirmed CTE cases and reported on 3 additional CSTE cases, noting the overall athletic makeup of the subjects: 43 boxers, 5 American football players, 1 professional wrestler, and 1 soccer player. This report also explored the timeline of CTE symptomology, finding that symptoms of half of the athletes were observed within 4 years of their retirement, often while they were in their early 40s, and continued to progress in an irreversible fashion.

In 2017, Mez and colleagues published results from a convenience sample of 202 deceased football players in which a very high proportion of players (87%) had neuropathological evidence of CTE, leading the researchers to hypothesize that prior participation in football may be related to the development of the disease [81]. Of the 202 deceased players, 3 out of 14 high school, 48 out of 53 college, 9 out of 14 semiprofessional, 7 out of 8 Canadian Football League, and 110 out of 111 NFL players were neuropathologically diagnosed with CTE. Neither of the two pre-high school players had evidence of the disease. Athletes with severe pathology were more likely to be involved in the highest level of play than those with mild CTE severity.

The phosphorylated tau (p-tau) protein pathology of CTE is typically classified into four stages, where stages I and II are "mild" and III and IV are "severe" [81–83]. Stage I consists of 1–2 isolated perivascular epicenters of p-tau neurofibrillary tangles and neurites located deep in the cerebral sulci of the frontal, temporal, or parietal cortices. Stage II is characterized by superficial neurofibrillary tangles located along the sulcal wall and gyral crests and three or more CTE lesions found in multiple cortical regions. P-tau pathology is widespread in stage III, with the greatest severity of neurofibrillary degeneration in the frontal and temporal lobes, concentrated in the depths of the sulci [82]. Neurofibrillary pathology is also seen in the amygdala, hippocampus, and entorhinal cortex. In stage IV, lesions and neurofibrillary tangles are spread through most regions of the cerebral cortex and brain stem, along with neuronal loss, gliosis, and astrocytic p-tau pathology [81].

Currently, CTE can only be definitively diagnosed by a post-mortem neuropathological examination [83]. Distinctive clinical features, however, do exist that often follow a progressive course. In a study by McKee and coauthors [82], the clinical symptoms of each stage of CTE were recorded using medical record review and family interviews. They found that in stage I, four out of six subjects reported headache and loss of attention/concentration, two had trouble with executive function and explosivity, and three had short-term memory problems, depression, and aggressive tendencies. In stage II, individuals reported loss of attention/concentration, short-term memory loss, depression and mood lability, headache, and explosivity. Executive dysfunction, language difficulties, impulsivity, and suicidality were also present, although less common. In stage III, individuals most commonly reported symptoms of explosivity, attention/concentration difficulties, and executive dysfunction. Depression and mood swings, aggression, and visuospatial problems were also frequently found at this stage, as well as the less common symptoms of apathy, headaches, suicidality, and impulsivity. Seventy five percent of the stage III subjects were cognitively impaired. Finally, stage IV clinical symptoms included executive dysfunction, profound loss of concentration/attention, paranoia, depression, gait and visuospatial difficulties, and explosivity and aggressive tendencies. All subjects in stage IV developed severe memory loss with dementia during their course [82].

Mez and coauthors [81] found similar results with regard to a progressive clinical course of symptoms with CTE. Behavioral and mood symptoms were common in athletes with both mild (96%) and severe (89%) CTE pathology. Their study examined 111 cases of standardized informant reports of clinical symptoms finding that 48 (43.2%) individuals first presented with behavioral or mood symptoms, 47 (42.3%) first

presented with cognitive symptoms, and 16 (14.4%) initially presented with both behavioral or mood and cognitive symptoms.

It is crucial to note that the clinical presentation of CTE is separate from the accumulation of symptoms attributed to post-concussive syndrome, or other long-term sequelae of concussion, as CTE symptoms are due to progressive neuronal death and/or progressive decline in functioning neurons [84]. For example, when neuronal death occurs in a certain region of the brain, symptoms may present that coincide with that region's function. It is common for symptoms to appear in midlife, often years after the end of the traumatic exposure(s). Symptoms typically present slowly and gradually, often over decades, and broaden in scope and severity over time [84].

While repetitive brain trauma is the most notorious risk factor for the development of CTE, other risk factors may include genetics, family history, chronic inflammation, type of brain trauma exposure, age and duration of brain trauma exposure, frequency of brain trauma exposure, gender, race, and cognitive reserve [84]. It is currently unclear whether symptomatic hits that lead to concussions are riskier than sub-concussive hits that remain asymptomatic but accumulate over time [81]. It is also unclear whether specific biomarkers exist for CTE diagnosis. Recent research has suggested that CCL11 (a chemokine that has been associated with age-related cognitive decline) may be a potential diagnostic biomarker in the brains and CSF of people with CTE [85]. Cherry and coauthors examined the level of expression of CCL11 in the dorsolateral frontal cortex of subjects with neuropathologically verified Alzheimer's disease, CTE, and normal controls and found that the total levels of CCL11 were significantly elevated in those with CTE as compared to the subjects with Alzheimer's disease or the controls. This increase was also correlated with years of exposure to American football – CCL11 levels were significantly increased in subjects with CTE and exposure to 16 or more years of American football, as compared to controls with no exposure to sports and subjects with CTE and less than 16 years of exposure. Furthermore, using post-mortem CSF samples, a trend was found in which increased CCL11 levels were present in those with CTE but not Alzheimer's disease, compared with controls [85]. Hopefully, with ongoing research and public awareness, preventing the onset of CTE will be possible.

Differences Due to Age and Developmental Level

Age differences in concussion diagnosis and management were not given much attention until the early 2000s when studies began to reveal marked differences in the way that youths and adults respond to and recover from concussions. Multiple studies have now shown that high school athletes require more time to recover cognitive performance than collegiate athletes [86–88], even though collegiate athletes had a greater prior incidence of concussion, which typically slows recovery [89]. Lovell and colleagues (2003, 2004) revealed a heightened vulnerability to concussions in younger athletes (ages 13–17 years), leading them to propose that currently accepted RTP guidelines for adults may be too liberal for adolescents. It has been suggested that the immature brain's sensitivity to glutamate [90, 91], a neurotransmitter involved in the metabolic cascade following concussion, may partly explain these differences in recovery time [92]. In addition, the young brain is still developing and differs from the adult brain in many areas including the brain water content, amount of myelination, total blood volume, structure of the blood-brain barrier, metabolic rate of processing glucose, level of blood flow, amount of synapses, and elasticity of the skull itself [93]. These findings collectively suggest that clinicians need to exercise increased caution in returning young athletes to play following a concussion or display of concussive symptoms.

Triage and Treatment

It should be noted that most people recover successfully from a concussion with no noticeable long-term effects. McCrea [51] found that 91%

of concussed football players returned to their pre-injury baselines within a week following injury. Nevertheless, the severe conditions that can result from sports head injuries in a small but noteworthy number of cases highlight the necessity of taking concussions seriously and being conservative in RTP guidelines.

The frequency of concussive sports injuries has encouraged the development of easy-to-administer neurocognitive tests that can be given on the sidelines of a playing field, immediately after a suspected concussion, to improve diagnostic accuracy. Of the neurocognitive tests reported in the literature, the Standardized Assessment of Concussion, or the SAC, is possibly the most popular and well-studied. The SAC takes approximately 5 minutes to administer, requires no prior experience in neuropsychological testing, and consists of four components: orientation, immediate memory, concentration, and delayed recall [94]. An assessment of strength, sensation, and coordination is included, as is the documentation of LOC, retrograde amnesia, and post-traumatic amnesia. The total composite score on the exam has been shown to be sufficient in differentiating between non-concussed controls and players who have suffered even mild concussions. A study of this test in 141 high school football players demonstrated that its demanding cognitive measures could be sensitive enough to detect mild concussions [94]. These findings were later supported by a larger study of 568 high school and college football players [95]. Normative data from more than 2500 male and female junior high, high school, college, and professional athletes have shown that the SAC is reliable over repeated administrations and is free of significant gender effects. It is also acceptable for use at all competitive and educational levels [96].

In addition to the SAC, the Second International Symposium on Concussion Prague 2004 developed a sideline assessment entitled the Sport Concussion Assessment Tool, or the SCAT [97]. The SCAT was created by combining several common tools into one standardized test and includes a neurologic screen, cognitive and memory assessments, and a query of symptoms, such as LOC, convulsive activity, and balance problems. The SCAT was updated to include the calculation of the SAC score and the Maddocks questions for sideline concussion assessment [98, 99]. The SCAT-3 was later developed to improve upon the reliability and sensitivity of the SCAT by adding a Glasgow Coma Scale, as well as assessments of symptom severity, neurocognitive function, and balance function [100].

In 2016, the Berlin meeting of the Fifth International Consensus Conference on Concussion in Sport led to the development of the SCAT-5. The SCAT-5 improves upon the SCAT-3 by clarifying administration and RTP guidelines. It states that the test needs at least 10 minutes to be appropriately administered, that the athlete should be in a resting state while completing the symptom checklist, and that a written clearance by a healthcare professional is needed before the athlete may RTP. The SCAT-5 also includes additional assessments, such as the Rapid Neurological Screen, which evaluates an athlete's speech, balance, visual tracking, cervical exam, reading abilities, and finger-to-nose coordination [101].

The military used SCAT metrics to develop the Military Acute Concussion Evaluation (MACE), which is used by combat medics and corpsmen on the battlefield to evaluate service members in whom a concussion is suspected [102, 103]. The MACE uses many of the same examination tasks as the SAC as well as includes a collection of demographic and injury incident details. The SAC, MACE, and Maddocks questions are summarized in Table 2.

Considering that balance is often affected by concussive injuries, neurological assessments would be improved by including clinical balance tests [48]. Balance, or the maintaining of the body's center of gravity, is controlled through a complex connection of neural networks within the brain involving the cerebral cortex, cerebellum, brain stem, and spinal cord. An incorrect interaction at any point within this system can cause failure to maintain proper balance. The Balance Error Scoring System (BESS) is a cost-effective, easily administered, quantifiable test designed to determine balance deficits obtained after a potentially concussive event [48]. To administer it, one needs

Table 2 Immediate assessments for concussion

Assessment	SAC	MACE	Maddocks questions
Orientation			Which field are we at? Which team are we playing? Who is your opponent at present? Which half/period is it? How far into the half is it? Which side scored the last touchdown/goal/point? Which team did we play last week? Did we win last week?
	Month, date, day of the week, year, time	Month, date, day of the week, year, time	
Immediate memory			
	Recall a list of five words immediately, three trials	Recall a list of five words immediately, three trials	
Concentration	Reverse strings of digits (3–6 digits in length)	Reverse strings of digits (3–6 digits in length)	
	Reverse the months of the year	Reverse the months of the year	
Delayed recall	Recall list of five words 5 minutes later	Recall list of five words 5 minutes later	
Neurologic screening	Recollection of injury, strength, sensation, coordination	Pupil size and reactivity, speech fluency and word finding, pronator drift, gait and coordination	
Exertional measures	40-yard sprint, 5 sit-ups, 5 push-ups, 5 knee bends	None	

Data from Coldren et al. [103], Maddocks et al. [99], McCrory et al. [149]
The SAC and Maddocks questions are typically used for sideline assessments for sports injuries; the MACE was developed for battlefield screening for military personnel suspected of concussion

only a stopwatch and a piece of foam. Athletes are asked to stand with their hands on their hips and their eyes closed for 20 seconds in each of three stances – double, single, and tandem – first on solid ground and then on a piece of foam. An error is recorded if the athletes step, stumble, fall, lift their foot, lift their hands off their hips, open their eyes, or flex or abduct their hips more than 30°, and do not correct their footing within 5 seconds [48]. A study by McCrea [104] found that after a concussive event, a change from baseline scores in the BESS averages 5.7 points initially and then 2.7 points at 1 day. There are limitations to the BESS: an effect of fatigue, ankle instability, and learning or practice has been observed after repetitive administration [105–107]. Despite these limitations, the use of a comprehensive sideline assessment, like the BESS, that considers neurological and balance function should be conducted whenever an athlete is suspected of sustaining a concussion.

In addition to neurocognitive testing, neuropsychological testing is becoming common among sports health professionals. The wide range of tests currently available is sensitive to concussive impairments. The conventional neuropsychological assessments include the Trail Making Tests A and B [108], Digit Symbol Substitution Test [109], Controlled Oral Word Association (COWA) Test [110], Hopkins Verbal Learning Test [111], and Stroop Word Color Test [112]. There are also computerized assessments available, which include the Automated Neuropsychological Assessment Metrics (ANAM) [113], Axon Sports (Scottsdale, AZ, USA; formally, CogState Ltd.'s CogSport©) [114], Headminder Cognitive Stability Index (CSI) [115], BrainCheckers test (Behavioral Neuroscience Systems, Springfield, Missouri, USA) [116], CNS Vital Signs test [117], Immediate Post-Assessment of Concussion Test (ImPACT Applications®, San Diego, CA, USA) [118], and Defense Automated Neurobehavioral Assessment (DANA) [119] (Table 3). With advancing technology and increased access to hand-held devices, companies have begun to develop easily downloadable applications to assist in sideline assessments of concussions. Cleveland Clinic, for example, developed the C3 application (Cleveland Clinic Concussion) to use as a tool for assessing concussive symptoms and guiding therapy and recovery for individual athletes [120]. Other applications include the CRR (Concussion Recognition and Response™, PAR

Table 3 Conventional tests for assessment of mild head injury

Assessment	Description
Trail Making Tests A and B	Part A involves drawing lines between 25 numbered circles, in sequential order, which are randomly arranged. Part B requires subjects to connect circles containing the letters A through L and numbered 1 through 13 by drawing lines alternating between numbers and letters in sequential order Subjects are instructed immediately on their mistakes and continue from the last correct circle. The test takes approximately 5–10 minutes to complete. The test evaluates information processing speed, visual scanning ability, integration of visual and motor functions, letter and number recognition and sequencing, and the ability to maintain two different trains of thought
Digit Symbol Substitution Test	Paper-pen test consisting of digit symbol pairs followed by a list of digits. The subject writes as many of the corresponding symbols on the list of digits as possible within the allowed time. Is sensitive to brain damage
Hopkins Verbal Learning Test-Revised	Verbal learning and memory test requiring the use of both working and episodic memory. Subjects are asked to recall a repeated list of words several times. The words fall into discrete categories. Learning ability and total immediate recall and delayed recall are recorded
Controlled Oral Word Association (COWA)	Spoken word test. The examinee has 1 minute to name as many words as possible that begin with particular letters. Examinee is then given 1 minute to name as many animals as possible. This test is a measure of verbal fluency, specifically for letters, requiring initiation and maintenance, both considered to be aspects of frontal lobe function
Stroop Word Color Test	Provides diagnosis of brain dysfunction and the evaluation of stress, personality cognition, and psychopathology. Assesses cognitive flexibility, resistance to interference from outside stimuli, creativity, and psychopathology by requiring subject to read through words, name ink colors of symbols, and name ink colors of color words that do not match. Five minutes to administer
Automated Neuropsychological Assessment Metrics (ANAM)	Computer-administered neuropsychological battery. Specifically designed for military use. Consists of 9 subtests and a questionnaire of symptoms. Assesses energy-fatigue level, predominant mood state, visuomotor response timing, visual search, sustained attention, working memory, processing efficiency, computational skills, spatial processing, and visuospatial working memory
Braincheckers	Computer-administered neuropsychological battery. Consists of 6 subtests and a questionnaire of symptoms. Assesses energy-fatigue level, predominant mood state, visuomotor response timing, visual search, sustained attention, working memory, processing efficiency, computational skills, spatial processing, fronto-executive functioning, and visuospatial working memory
CogState Sport	Battery of four card-based games. Assesses psychomotor function, processing speed, visual attention/vigilance, visual learning, and memory
Headminder Cognitive Stability Index (CSI)	Web-based neurocognitive test protocol. Subtests relevant to general cognitive screening techniques. Adaptable for repeatable, longitudinal assessments. Ten subtests; 30 minutes in length
CNS Vital Signs	Computerized neurocognitive test battery. Comprised of seven tests: verbal and visual memory, finger tapping, symbol digit coding, the Stroop Test, a test of shifting attention, and the continuous performance test. Sensitive to malingerers and patients with conversion disorder. Suitable as a screening instrument
Immediate Post-Assessment of Concussion Test (ImPACT)	Computerized neuropsychological test battery. Six individual cognitive test modules assess cognitive functioning, including attention, memory, reaction time, and processing speed. Modules include word memory, design memory, Xs and Os, symbol match, color match, and three letters. Composite scores are derived in the areas of memory, reaction time, and processing speed
Defense Automated Neurobehavioral Assessment (DANA)	Portable neurocognitive assessment tool administered on an android device. There are three different versions with varying lengths: DANA Rapid (5 minutes), DANA Brief (15 minutes), and DANA Standard (45 minutes). Depending on the battery chosen, assessments include simple reaction time, procedural reaction time, go/no go, spatial discrimination, code substitution simultaneous, code substitution delayed, Sternberg memory search, matching to sample, insomnia screening index, primary care PTSD screen, patient health questionnaire, Pittsburgh sleep quality index, combat exposure scale, PTSD checklist military version, and the deployment stress inventory

Inc., Lutz, FL, USA), the Concussion App from Sports Safety Labs LLC, and Play It Safe from Concussion Health LLC [121].

The popularity of sideline assessment tests has increased, thanks to research showing a need to assess higher cognitive functioning directly, rather than by relying on reports of LOC and amnesia. One study found that the presence of amnesia, not LOC, was most predictive of difficulties 3 days post-injury [122]. Similarly, another study found that impairment of immediate recall was much more frequent than disorientation post-injury and suggested that evaluating cognitive function and disability by asking the concussed athlete to state the day, time, month, and year may not be the most clinically useful evaluation task [123]. A third study found that athletes who reported memory problems following injury had significantly more symptoms, longer durations of symptoms, and significantly decreased performances on neurocognitive testing [115]. These results indicate that the conventional focus on LOC and disorientation as predictors for severity of a concussion may be misplaced. Moreover, with LOC occurring in less than 10% of sports-related concussions, it is essential to instead evaluate memory and immediate recall following suspected concussion [122].

In their NCAA Concussion Study, McCrea and colleagues [51] examined the timeline of concussive injury symptoms in 1631 football players from 15 US colleges. They found that the most severe symptoms occurred immediately after concussion and were followed by a recovery period lasting 5–7 days. Normal cognitive functioning often returned by day five after injury, whereas a full 7 days were needed for clinical symptoms to return to baseline and control levels (Fig. 1). This large cohort study supported the clinical experience of many professionals and contributed scientific evidence to RTP guidelines by suggesting a gradual reintroduction to sport over the course of several days to weeks, depending on the severity of injury.

Despite growing research and interest in addressing sports concussions, there is still little consensus in the field on the best approach to post-injury care, especially regarding when and how to return athletes with head injuries to play. Hunt and Asplund [124] suggest that whatever assessment tools are used should include a cognitive assessment, some measure of balance testing, and a self-reported symptom assessment. Many guidelines promote allowing athletes to recover from all symptoms before testing, so as to prevent learning effects. In the US military, exercise to a target heart rate is recommended prior to neurocognitive testing to assess whether clinical symptoms, such as headache, have fully resolved [125]. Many institutions have started mandating baseline neurocognitive testing for

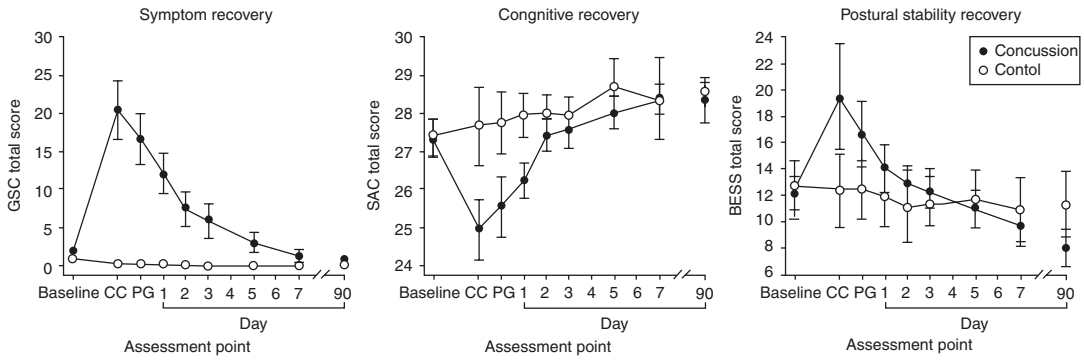

Fig. 1 Symptom, cognitive, and postural stability recovery in concussion and control participants. Higher scores on the Graded Symptom Checklist (GSC) indicate more severe symptoms; lower scores on the Standardized Assessment of Concussion (SAC) indicate poorer cognitive performance; and higher scores on the Balance Error Scoring System (BESS) indicate poorer postural stability. Error bars indicate 95% confidence intervals. CC indicates time of concussion; PG postgame/postpractice. On the BESS, multiple imputation was used to estimate means and 95% confidence intervals for control participants for the CC and PG assessments

athletes at risk of head injury to obtain an individualized standard in the event of a concussion, although there is little evidence that this approach changes clinical outcomes. These preseason baselines account for any comorbidities that may affect testing, such as learning disabilities, previous concussion history, medication usage, and mental conditions. While controlling for baseline performance is ideal, this current system of assessment can be circumvented; athletes have reported intentionally underperforming on these tests to decrease the scores needed for them to RTP post-injury [126].

The decision about when to return an athlete to play without limitations is an issue of considerable importance in the sports medicine field, especially given the potential for external or internal pressures on an athlete to return prematurely. There are many published guidelines in the literature, but they are based largely on clinical experience and expertise in the field rather than on rigorous study and objective evidence. Most guidelines currently recommend a gradual, stepwise return to full activity that is overseen by a qualified health professional and begun only after the athlete has become asymptomatic. If an injured athlete exhibits symptoms with increased activity, then the athlete is returned to a previous step in the recovery process, such as rest. In November 2008, the guidelines proposed by the 3rd International Conference on Concussion in Sport in Zurich, Switzerland [98], improved upon the guidelines presented by prior conferences in Vienna, Austria [127], and Prague, Czech Republic [97]. The recommendations of the Zurich conference are presented in Table 4.

Research on the effect of multiple concussions has prompted clinicians to differentiate RTP guidelines based on the severity of the concussion and the athlete's concussion history. Guidelines by Cantu [128], which are now outdated, are presented in Table 5. For the purposes of historical background, at that time the concussion grades in these guidelines included Grade 1, no LOC and post-traumatic amnesia (PTA) or post-concussive symptoms lasting less than 30 minutes; Grade 2, LOC less than 1 minute and PTA or post-concussive symptoms 30 minutes to 24 hours in duration; and Grade 3, LOC lasting more than 1 minute or PTA lasting longer than 24 hours with post-concussion signs or symptoms lasting longer than 7 days [128]. This system was revised from his previous grading system [41] based on evidence from prospective studies on PTA and persistence of post-concussive symptoms. Several other grading systems for concussion also exist in the literature. Those commonly cited are the Colorado Medical Society [129], the American Academy of Neurology [130], Jordan B.J. [131], Ommaya [132], Nelson [133], Roberts W.O. [134], and Torg Grading Systems for Concussion [135].

During early 2013, when concussion became a topic of popular discussion, multiple new and

Table 4 Zurich Guidelines, Graduated Return-to-Play Protocol

Rehabilitation stage	Functional exercise at each stage of rehabilitation	Objective of each stage
No activity	Complete physical and cognitive rest	Recovery
Light aerobic exercise	Walking, swimming, or stationary cycling, keeping intensity to 70% of maximum predicted heart rate; no resistance training	Increase heart rate
Sport-specific exercise	Skating drills in hockey, running drills in soccer, no head impact activities	Add movement
Noncontact training drills	Progression to more complex training drills, e.g., passing drills in football and ice hockey; may start progressive resistance training	Exercise, coordination, and cognitive load
Full-contact practice	Following medical clearance, participate in normal training activities	Restore athlete's confidence; functional skills
Return to play	Normal game play	

Used with permission from McCrory et al. [149]
Athlete should continue to the next level if asymptomatic at the current level. Generally, each step should take 24 hours, so that an athlete would take approximately 1 week to proceed through the full rehabilitation protocol once asymptomatic at rest and with provocative exercise. If any post-concussion symptoms occur while in the stepwise program, then the patient should drop back to the previous asymptomatic level and try to progress again after a further 24-hour period of rest has passed

Table 5 Cantu Guidelines for Return to Play (RTP) After Concussion

	First concussion	Second concussion	Third concussion
Grade 1 (mild)	May RTP if asymptomatic for 1 week	RTP in 2 weeks if asymptomatic at that time for 1 week	Terminate season; may RTP next season if asymptomatic
Grade 2 (moderate)	RTP after asymptomatic for 1 weeks	Minimum of 1 month; may RTP then if asymptomatic for 1 week; consider terminating the season	Terminate season; may RTP next season if asymptomatic
Grade 3 (severe)	Minimum of 1 month; may RTP if asymptomatic for 1 week	Terminate season; may RTP next season if asymptomatic	

Used with permission of Elsevier from Cantu [150]
Note. Asymptomatic means no headache, dizziness, or impaired orientation, concentration, or memory during rest or exertion

updated guidelines and position statements were published. These updated guidelines were generated by groups like the American Medical Society for Sports Medicine, the American Academy of Neurology (Box 1), and the Zurich Consensus. All three groups agreed that no single assessment test can be used to determine the occurrence of a concussion but that any athlete who is suspected of having a concussion should be removed from play immediately [136]. In addition, the consensus was that there is no golden rule for returning an athlete to play. All athletes should be treated on an individual basis following a gradual stepwise RTP routine that allows the athlete to advance to more strenuous activities only once the athlete is asymptomatic at the current level [136].

Box 1 American Academy of Neurology Guidelines for Return to Play (RTP) After Concussion

1. Athletes must be assessed by an experienced LHCP with training both in the diagnosis and management of concussion and in the recognition of more severe TBI before returning to play.
2. Persons supervising athletes should prohibit any athlete with concussion from RTP/practice (contact-risk activity) until the athlete is asymptomatic.
3. Persons supervising athletes of high school age or younger with diagnosed concussion should treat them more conservatively than older athletes regarding RTP.

Data from Giza et al. [151]

Neuroimaging and Concussions

Computed tomography (CT) and magnetic resonance imaging (MRI) remain the imaging techniques of choice for initial assessment of acute head injury for skull fractures and intracranial hemorrhage. MRI is the also standard of care for the evaluation of subacute or chronic traumatic brain injury [137]. Despite the use of these modalities, the neuroimaging of concussions has not been thoroughly explored; most mTBIs/concussions do not result in abnormalities that can be detected by either CT or standard MRI studies [138]. Research has suggested that less than 10% of patients with minor head injuries have positive CT findings and that less than 1% require neurosurgical intervention [139]. The resulting reliance on neurocognitive testing and symptom checklists for concussion diagnosis has motivated clinicians and researchers to use advanced imaging techniques to better quantify and define structural injuries in the brain following concussion. Possible techniques with increased sensitivity over traditional neuroimaging modalities include MR diffusion tensor imaging (DTI), functional MRI (fMRI), magnetic resonance spectroscopy (MRS), and positron emission tomography (PET). DTI provides a measurement modality for white matter integrity and connectivity. Functional MRI offers the opportunity to receive real-time feedback on cerebral metabolism and brain activation patterns during specific cognitive or motor tasks. MRS and PET provide images that indicate

functional cerebral metabolism. Each of these modalities, however, requires relatively long collection times and, with the exception of PET, requires post-imaging data processing. These advanced imaging technologies are not currently used in clinical assessments of sports concussions but may play a future role with increased investigation.

Early studies have used advanced imaging modalities in a research setting to observe brain changes in soccer players without a history of symptomatic concussion and compared results to images of brains from athletes participating in noncontact sports. In a small study of soccer players and swimmers, advanced DTI demonstrated increased radial diffusivity in the brains of the soccer players only – a finding similar to what may be observed in persons with mTBI [32]. Further, a study using MRS found neuroinflammatory changes among former professional soccer players and not in matched noncontact sports athletes (table tennis players, runners, and ballroom dancers) [33]. Additionally, a study by Lipton and coauthors [34] observed microstructural abnormalities in the temporo-occipital white matter of amateur soccer players that was associated with poorer memory performance on neurocognitive tests. These findings suggest that repetitive subconcussive head impacts may lead to brain changes detectable by neuroimaging techniques, but further study into the specificity and sensitivity of these techniques is certainly needed.

Prevention

Prevention of sports-related concussions needs to be encouraged through further education of players, coaches, and referees, as well as through the use of research-based guidelines by sports health professionals. The teaching of safe athletic techniques, promotion of protective equipment, and encouraging of symptom reporting could further decrease the incidence and consequences of concussions.

Take the sport of football as an example. Mueller and Schindler [140] noted that coaches and referees must do a better job of emphasizing and enforcing the rules against targeting the head as an initial contact point and tackling head on. The latter rule protects the impacted player by decreasing the contributing torso mass of the tackling player, through a "head-up" stance, resulting in lower effective mass and lower force on the impacted player, presumably lowering the risk of concussion in the player being struck [141]. It is particularly important to decrease the force on the impacted player since a study of NFL athletes found concussions occurred in the impacted and not the tackling players [123]. The difference in force with proper tackling technique translates directly to a difference in peak head acceleration, which was found to be statistically correlated to whether a collision resulted in a concussed or an uninjured player [123].

Other rules, such as the kickoff distance, have also been changed in hopes of reducing the number of concussions reported each season. In 2011 the NFL moved the kickoff spot up 5 yards to cause more touchbacks and less returning of the ball. Kickoff returns are chaotic and one of the most violent plays in football. Due to this rule change, concussions that occurred on kickoffs decreased from 35 in the 2010 season to 20 in the 2011 season [142]. Currently college teams, such as those in the Ivy League, are implementing no-contact practices to reduce the amount of injuries players incur by hitting their own teammates. Since eliminating tackling at practices, players are experiencing fewer concussions, as well as fewer shoulder and neck injuries. Moreover, players are becoming better at tackling: by focusing on avoiding head collisions, the number of missed tackles in games has fallen by more than half [143].

In addition to adjusting tackling techniques, improved helmet design has been shown to reduce the incidence of concussion in football. Rowson and colleagues [144] explored the impact of helmet design on concussive injury by using helmet-mounted accelerometer arrays to collect head impact data on 1833 collegiate football players. They found that players wearing Revolution helmets sustained significantly fewer concussions per head impact than players wearing VSR4 helmets (3.86 vs. 8.37 concussions per 100,000 impacts, respectively). Since the

Revolution helmets allow less head acceleration post-impact than the VSR4 helmets, designs to minimize head acceleration may help to protect against concussive injury [144]. It is important to note that, in this study, several authors had a financial interest in the instrumentation used to collect the biomechanical data.

Like helmets, the use of headgear has been suggested to decrease the incidence of concussions. In the sport of soccer, for example, athletes who have previously sustained concussions, goalies, and children have been advised to wear headgear during practices and games [145]. A cross-sectional study of soccer players ages 12–17 years found that a total of 47.8% of players might have sustained a concussion (based upon self-report of symptoms which was extrapolated to a diagnosis of concussion based upon the symptoms) during a single season. Out of these athletes, 52.8% were not wearing headgear and 26.9% were wearing headgear [146]. Further research is needed to deduce the ability of headgear to decrease the incidence of concussions in non-helmet wearing athletes.

Another approach to preventing sports-related concussions may lie in strengthening the neck muscles of athletes. In a single study of 6704 high school athletes, Collins C.L. and colleagues [147] found that overall neck strength served as a significant predictor of concussion, even after adjusting for gender and sport. In fact, the odds of concussion decreased by 5% for every 1 pound increase in neck strength. By measuring neck strength, one might be able to identify athletes at a higher risk of concussion and use this information to both educate players and coaches and inform strength-training regimens.

To prevent worsened symptoms or second injuries post-concussion, athletes need to be immediately removed from play and evaluated by a qualified health professional. To do this, players need to be educated on how to recognize symptoms suggestive of a concussion as well as encouraged to report suspected injuries to coaches and other players. Kroshus and coauthors [40] explored concussion reporting in 328 male and female collegiate athletes and found that almost half of those surveyed reported continuing to play in a game or practice despite experiencing post-impact symptoms consistent with a possible concussion. Moreover, one-quarter of those surveyed reported being pressured by their coaches, teammates, fans, or parents during the previous year to continue playing after a head impact [40]. Clearly, progress needs to be made in encouraging athletes to report their symptoms immediately and in creating an environment of health advocacy within athletics, not only at the collegiate and professional levels but also in youth, elementary, middle, and high school levels of play.

Areas for Future Research

Public interest in sports concussions has increased research in the area; however, many details about the mechanisms, etiologies, and best treatments of concussive injuries remain understudied. Both large-scale studies and anecdotal evidence from practitioners indicate that the great individual variability of the human brain significantly contributes to differences in concussion incidence and resolution. Further research will do best to explore the effect of specific comorbidities, as well as hereditary and environmental factors, on an individual's risk for and recovery from concussion. Screening has improved to allow practitioners to better assess injury on the sidelines, to request additional neurocognitive testing, and to supervise RTP regimens. For any tests to be useful, however, they must continue to be validated in different populations and to incorporate new technologies. Otherwise, some tests may remain inapplicable for a wide population of athletes or difficult to either administer or evaluate. As research continues to improve advanced neuroimaging of concussive injury, these modalities will also begin to play a role in clinical care, helping to improve the treatment and prognosis of concussive injury.

Conclusions

The complex and wide-ranging presentation of concussions make the study and care of concussed athletes an important issue for the medical

community. With recent studies elucidating the potential long-term effects and increased future risks caused by concussive injuries, it is our hope that increased awareness among the public and medical professionals will lead to the evolution and application of evidence-based practices for the diagnosing and treating of concussions. Since concussion is perhaps the single most common form of acquired brain injury in the young and middle-aged, it is imperative that health providers, sports professionals, and athletes themselves develop a better understanding of the risks, prevention, diagnosis, and treatment of sports concussions.

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Blast-Related Concussion

Carson T. Lawall

Introduction

Neurological consequences of blast-related injury have been described in medical literature as early as World War I (WWI) [1]. WWI was the first major conflict that led to blast injury on a large scale. Soldiers engaged in trench warfare were subjected to frequent artillery attacks, and the majority of deaths in the World War I were due to blast injury. In this setting, several blast-exposed soldiers would describe events consistent with a concussion [2]. The diagnosis of "shell shock" was an attempt to describe cases where patients had neurological symptoms in the context of a blast exposure. However, as time progressed, there grew concern that the symptoms may have been more psychological rather than organic in nature [2]. It has been historically recognized that both physical and psychological factors may play a role in symptomatology following concussion [3]. This observation continues today and still engenders debate. In clinical practice, both in the theater of war and in following patients who have returned from the battlefield, consideration of physical and psychological factors is important in the evaluation of symptoms seen after a blast-related concussion. The diagnostic difficulties faced today in regard to concussion and the overlap of psychological symptoms have also been described in the past, as well as concerns about the sensitivity and specificity of the available diagnostic tests [3]. The issue of limitations of available diagnostic testing continues despite the array of advanced medical technology at our disposal.

Changes to the tactics on the modern battlefield and improvements in personal protective equipment, body armor, and vehicles have protected against injuries that would have previously been fatal [4, 5]. More severe injuries are averted, but non-life-threatening injuries, such as concussion due to blast injury, have again become a major concern. While determining the number of concussions that occur in a theater of war does have some methodological issues, the number of patients who have suffered a concussion while deployed in Operation Enduring Freedom/Operation Iraqi Freedom is estimated to be between 225,000 and 370,000 [6–10]. Of those injured, many are due to blast exposure. This may account for up to 78% of injuries to service members in Iraq and Afghanistan [11, 12]. Given the large numbers of patients involved, this represents a significant long-term health concern [13].

Historical Perspective

Injury due to blast exposure is not specific to modern warfare. There are several parallel experiences seen with the conflicts in Iraq and

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Afghanistan with trench warfare seen in WWI. In all three conflicts, blast exposure is the primary means of injury to soldiers, sailors, marines, and airmen. In WWI, the explosives were generally delivered by artillery and mortars [2], and in current conflicts, explosive injury is most often delivered by the improvised explosive device (IED) [13], but the physical effects are the same.

An estimated 60% of deaths in WWI were due to shrapnel or fragmentation wounds [2], which suggests that explosives accounted for a large proportion of the survivable injuries sustained by soldiers. In WWI, patients exposed to shelling and blasts reported symptoms of headaches, amnesia, difficulty concentrating, dizziness, tinnitus, and sensitivity to noise. Many of these patients by today's definition would meet clinical criteria for concussion [2, 14]. This constellation of symptoms, combined with blast exposure, was termed "shell shock." Originally, these symptoms were thought to be due to a structural lesion caused by the compressive forces of the blast wave [2, 15], and based on descriptions of early cases, some exposures did appear to cause structural damage leading to neurological deficits [1]. However, as understanding evolved, it became clear that some patients who did not have concussions or had minor injuries also had similar symptoms, and in most cases, these symptoms could not be linked to an organic lesion. As these complaints are non-specific and common to multiple disorders, various explanations for their occurrence appeared. Research into the stresses of trench warfare yielded more information and contributed to further observations that many patients with shell shock did not actually have significant exposures to blasts [2]. Despite research, resources, and attempts at treatment in forward areas, shell shock remained a common phenomenon. It has been estimated that 10% of battle casualties were categorized as shell shock or neurasthenia in WWI. One-seventh of all discharges from the British army were due to shell shock, and 32,000 war pensions were awarded for shell shock, which increased with time as it became popularized in the public. Interestingly, while advocating for those who were injured or disabled by their experience in warfare, involvement of the lay media in support of individual veterans possibly distorted policy and research [2], which complicated conclusions about the true nature of the injury.

In WWII, to avoid the epidemic of shell shock, the term was actually banned, but the common symptoms experienced by soldiers continued. In 1939, the term "post-concussional syndrome" was introduced to describe the symptom complex. In WWII, it was also recognized that distinguishing symptoms caused from blast-concussion versus another etiology was difficult both clinically and with the available diagnostic testing. At the time, diagnostic testing was largely in the form of X-rays, pneumoencephalogram, and electroencephalogram, which were neither sensitive nor specific for the diagnosis of disorders related to concussion [2, 6].

Soldiers also were much more likely to attribute symptoms to shell shock as there was no stigma attached to the diagnosis. Patients and the public could identify with the condition, which was considered to be a neurological diagnosis, and not feel that a negative label was implied by the description. This may have benefitted patients by encouraging them to seek help; however, it may also have led to mistreatment if symptoms were attributed to concussion or shell shock, when other causes of such symptoms could have been treated more appropriately [2].

Understanding the history of blast-related injury may be helpful in interpreting some of the issues today. There is still stigma associated with psychological conditions in the military, where admitting anxiety or fears may be viewed as weakness, and attributing symptoms to mild traumatic brain injury (mTBI) is a much less stigmatizing option [2, 9]. Unfortunately, while it may be less stigmatizing, it is clear that beliefs about concussion and brain injury may actually affect recovery. Strongly held beliefs about brain injury or brain damage may play a role in maintenance of symptoms [2, 7, 16]. Today, there is also significant media coverage and an emotional component in

the debate about the consequences of concussion and blast-related concussion which may cloud the issue. At times, this can create difficulties in discussing symptoms and prognosis with patients. The information available in the lay media, as well as commonly held opinions, are not necessarily consistent with what has been demonstrated in the medical literature [7]. There is also an increased focus in the military on forward treatments of concussion in the form of diagnostic imaging available in the theater of war, increased number of specialists in neurology, and specialized concussion recovery centers. Just as it has in the past, diagnosis of concussion and post-concussive symptoms continues to be complicated by reliance on clinical symptoms, which have overlap with several other disorders including post-traumatic stress disorder (PTSD), depression, and migraine [2, 6–12, 17, 18]. Diagnostic tests, such as physical examination and computed tomography (CT) scanning, are not sensitive in making the diagnosis of concussion (and by definition must be normal in the setting of concussion). Newer modalities such as magnetic resonance imaging (MRI) have limited clinical use at this time due to issues with specificity and sensitivity, as well as limited prognostic application even in moderate and severe TBI [19–22]. Many of the problems and frustrations that complicate treatment of concussion and blast-related concussion today have also created difficulty in the past [2, 9].

Pathophysiology

Explosive blast may cause injury to the body via several different mechanisms (Box 1) [13]. The mechanisms leading to injury are divided into primary effects from the blast wave, secondary effects caused by projectiles or flying debris from the blast causing blunt or penetrating injuries to the body, tertiary effects from the body being thrown from the blast, and quaternary effects such as burns, asphyxia, and/or toxic exposures from the blast as well as exacerbation of previous illnesses [9, 12, 17, 23].

Box 1 Immediate effects of blasts and explosions

- Primary—direct effects (e.g., overpressurization and underpressurization), rupture of tympanic membranes, pulmonary damage, rupture of hollow viscera
- Secondary—penetrating trauma, fragmentation injuries
- Tertiary—effects of structural collapse and persons being thrown by the blast wind, crush injuries and blunt trauma, penetrating or blunt trauma, fractures and traumatic amputations, open or closed brain injuries
- Quaternary—burns, asphyxia, and exposure to toxic inhalants

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The primary mechanism is due to the blast wave and overpressurization [9, 11, 12, 17, 23]. The blast wave propagates from the point of detonation and dissipates with distance from the source. The blast wave is followed by a blast wind behind the initial shock wave, and is initially directed away from the blast, and then as the energy dissipates, reverses back to the point of detonation and causes underpressure. Injury results from barotrauma, which is a difference between pressure, either overpressurization or underpressurization, of the outer surfaces of the body and the internal organs [9, 17]. As the blast wave strikes an object, part of the blast wave is reflected back to the source and part of the blast wave is deflected away, but the majority of the energy is absorbed and propagated through the body. The energy propagates through the body as a high-frequency stress wave and a low-frequency shear wave.

The high-frequency stress wave may cause damage to tissue by implosion, spalling (cavitation caused by reflection of the blast wave at the interface of materials with different density/acoustic

impedance), or by pressure differentials. The low-frequency shear wave results from compression of the body wall and structures underneath. The blast wave, itself, may cause damage to internal structures and the brain parenchyma without external injury [24].

Distance from the point of detonation is an important factor as blast waves in an outdoor setting dissipate by the cubed root of the distance from the source. Those closest to the source will have significantly more overpressure effects than those at a distance [17]. Those in enclosed structures may have more injuries as a result of barotraumas than those in open spaces due to reflection of the wave off structures and multiple wave effects [13, 15, 23].

Air-filled organs and air–fluid interfaces are the most susceptible areas to blast wave damage [9, 15, 17, 24]. The tympanic membrane, lungs, and gastrointestinal (GI) tract are especially susceptible, with the tympanic membrane being the most easily injured with even minor increases in pressure [15, 17]. Physical pathological changes to the brain seen in TBI are frequently associated with pathological changes in other organs [24]. While the tympanic membrane is cited as the most frequently injured structure in a blast wave injury, rupture of the tympanic membrane is only partially helpful in determining the potential for injury to the brain or other organs [25, 26]. There are some conflicting data as to the association of tympanic membrane rupture with blast-related concussion. Tympanic membrane rupture is associated with loss of consciousness in blast exposure [17, 26], but is not sensitive as a marker for primary blast injury to the body. In a study of 167 patients exposed to blasts in Iraq, tympanic membrane rupture had only a 50% sensitivity as a biomarker for other primary blast injury, although it was fairly specific, with an 87% specificity in determining if there was sufficient force from the blast to cause injury to other organs [25]. By inference, one may consider the brain, which does not have air–fluid interfaces, more resistant to blast wave phenomena affecting the tympanic membrane [17, 24]; however, in clinical experience, the majority of patients with concussion (most often without loss of consciousness), due to blast, do not have damage to the tympanic membrane. This demonstrates the limits of its clinical utility as a biomarker for central nervous system (CNS) injury. Observation of tympanic membrane rupture is also complicated by the fact that simple ear protection may prevent injury to the tympanic membrane in blasts that otherwise would have enough energy to have caused more severe injuries [17].

Secondary and tertiary injuries are most likely similar to concussion caused by non-blast mechanisms of head trauma. Secondary injuries from objects projected from the blast may cause penetrating or blunt trauma [11, 17, 23], and one would expect a similar pattern of injury to the CNS. Tertiary injuries result from being thrown by the blast into other objects, and again, one would expect an injury pattern similar to that seen in other mechanisms of concussion [17].

Quaternary injuries are due to exposure to burns, chemicals, and additional variables which may occur in the setting of blast exposure [17, 23]. Conventional military ordinance releases light/electromagnetic, acoustic, and thermal energy as well as toxic fumes. The effect of these variables on the brain may be difficult to predict and may be different in each exposure. Additionally, the magnitude of effect is difficult to determine in the setting of other injuries [13]. Patients may have a contribution from one or all four injury subtypes, each of which may contribute to the overall pattern of injury [9]. This further complicates distinction from blast-related injury primarily from the blast wave itself, and additional or comorbid non-blast injuries.

One additional consideration is the environment in which the injury occurred. Blast injury in the combat setting is unlikely to occur in isolation. Frequently, service members are exposed to a blast when under extreme stress. While an IED blast may occur in isolation, it is common that the blast occurs when under direct or indirect enemy fire, or an IED is a prelude to a more coordinated attack. Those involved are often in life-threatening situations and are not only exposed to potentially deadly fire from enemy combatants but also may have suffered other wounds. In these situations, service members may be involved in vehicle

accidents or fires, may have to care for the wounds of their comrades, may see disturbing wounds suffered by comrades or the enemy, may have friends die in the attack, and may be forced to engage in combat and kill enemies. Each of these factors may have additional psychological consequences and likely contribute to symptoms seen after concussion.

Pathology

The pathology of blast-related concussion is largely described in animal models as concussion/mTBI in humans is not a fatal injury and is not amenable to direct pathological evaluation. There are some limitations in interpretation of animal findings as there are significant structural differences in mouse, rat, rabbit, or pig models that may lead to differences in how blast waves affect or propagate through the brain. Also, many models use high blast overpressures on anesthetized animals, which may be less consistent with mild injury, although there is evidence that even modest blast pressures may cause effects in the CNS [9]. One must be careful in interpreting data as in animals a more severe (moderate or severe TBI) may have resulted from the experimental exposure, which would be more difficult to distinguish clinically in an animal model. Mild blast injury in one study was considered to be an exposure to a shockwave that caused 5% mortality in animals in a supine position and no lethality in the prone position. In these animals, many of the injuries sustained were to the lung and liver [27]. While this is considered mild, it may represent a significant injury, as in human patients with concussion or mTBI related to blast, it is very rare to see lung or GI tract injuries.

Animal studies suggest that blast waves may have structural effects on the brain and have demonstrated alterations in physiology as well as microscopic structure following blasts [9, 11, 27]. In a porcine model, following a blast, there is transient flattening of the EEG and brief apnea, suggestive of brainstem effects. In a mouse model, the most common structures injured, as seen in pathological evaluations, were the cerebellar white matter, internal capsule, cerebral peduncles, and pyramidal fibers in the pons and medulla, but again, based on the protocol the severity of injury was likely greater than that seen in mTBI. Microscopically, one may see expanded perineuronal spaces, cytoplasmic vacuoles, myelin deformation, and axoplasmic shrinkage [9]. The findings in these models is felt to be most closely related to diffuse axonal injury [9, 24, 27]. There may also be temporary evidence of abnormal axonal transport after blast exposure in rats, which may contribute to the physical findings seen in these animals [9]. In mouse models, after a blast exposure, there is evidence of abnormal social interaction with other mice and behavioral changes; however, these often improve with time, and in one study, 2 weeks after the exposure, the mice showed the same interactions as mice exposed to a sham blast experience [27]. There may also be some evidence that pathological changes may not be permanent and improve in time, which may parallel clinical improvement in time in animal models [10, 28].

There are very little data in regard to pathological consequences of concussion/mTBI due to blast in humans [9]. Much data in regard to the immediate pathological consequences in humans are from moderate or severe TBI [9]. In patients who have died as a result of blast injury, microscopic parenchymal or leptomeningeal hemorrhages are the most commonly described finding. This can be seen throughout the cerebral white matter, in the corpus callosum, and in the basal ganglia. In a description of nine soldiers who died as a result of an atmospheric blast, with no evidence of external trauma, there was evidence of hyperemia in the brain and leptomeninges, and both microscopic hemorrhages, as well as in some cases larger hemorrhages, contusions, and in one case a laceration of the cerebellum with extensive hemorrhage [24]. Unfortunately, much of the data in regard to these pathological findings are based on rather old case series and did not describe findings consistent with diffuse axonal injury, although, since microhemorrhages are seen in diffuse axonal injury, one may postulate that diffuse axonal injury may have been present in these cases as well [24]. Given limited data in

the setting of mTBI, one could expect similar pathologic findings in human and animal models and likely similar changes in findings over time, but making definitive conclusions at this time is not possible.

Symptoms

Patients with blast-related concussion experience many of the same symptoms as those who have suffered a concussion by other means. Symptoms, such as headache, dizziness, vertigo, imbalance, difficulty concentrating, alteration in consciousness, confusion, seeing "stars," feeling "dazed," brief post-traumatic amnesia, loss of consciousness, blurry vision or transient double vision, nausea, vomiting, and/or insomnia are common to both blast- and non-blast-related concussions [9, 12, 16]. Additionally, blast-related concussion patients commonly also complain of ear pain, hearing loss, and tinnitus.

Acutely, psychological symptoms may present with difficult to differentiate features as many patients report a sensation of time slowing down, a near out-of-body experience, tunnel vision, diminished hearing, difficulty understanding, and confusion which may be related more to the experience than due to physical trauma [7]. This further complicates diagnosis and treatment. Confusion in the setting of extreme stress, combat, injuries, threat of physical injury, sleep deprivation, and rapid change in sensory environment (from calm and quiet to loud, smoke-filled, and chaotic) may be mistaken for symptoms caused by head trauma [7]. Blast-related concussion may have more psychological sequelae and may have a stronger association with PTSD [10, 29]. Patients without concussion but exposed to blast evacuated from theater for injuries did have more psychological symptoms than non-blast-exposed patients [30].

It is also important to be vigilant for other injuries in the setting of blast exposure. As discussed before, it is possible to have injuries without evidence of external trauma [24], and rupture of the tympanic membrane is not sensitive as a biomarker for additional injuries due to blast wave trauma [23, 25, 26]. A good clinical exam is often sufficient in evaluating for other areas of trauma, but laboratory evaluation and imaging (often in the form of CT) are helpful, especially if there are unexplained symptoms or findings on exam suggestive of other injuries.

Of note, in the literature, there is frequent discussion of concern about soldiers ignoring symptoms in order to return to the fight. Often these statements are found in the introduction of the papers discussing concussion/mTBI [31]. To the author's knowledge, there is no study that examines the incidence of over- or under-reporting of post-concussive symptoms in the deployed setting. While this does occur, clinical experience in Kandahar, Afghanistan, from December 2010 to August 2011 is that under-reporting symptoms is actually quite infrequent, and the opposite appears to be much more common. This may be an artifact of observations at the NATO Role III hospital in Kandahar (a referral center for more complex cases), but in this setting it is a very small minority of patients that minimize somatic symptoms in order to return to combat. Other neurologists (in Kabul, Kandahar, and Helmand Province) reported similar observations over the time period of 2010 to 2013. Most patients accurately report their symptoms and express concern that their experience is properly documented. A smaller but significant proportion overrepresent symptoms or have non-physiologic findings, such as elaborated past-pointing or gait disturbance or a decline in the MACE (Military Acute Concussion Evaluation, a battlefield concussion assessment tool modeled after the Standard Assessment of Concussion used on sports sidelines [32], which consists of three parts—history and symptom evaluation, cognitive score, and a brief neurological examination) score despite improvement in overall level of consciousness. Frequently, overrepresentation of symptoms is transient in the first few days after an injury and resolves spontaneously. This is simply an observation, but one could theorize that this may be a result of changing perceptions of symptoms, feelings of reassurance as recovery progresses, or a result of validation once a patient has been evaluated and his/her

injury is recognized. An additional minority (albeit one that can take a disproportionate amount of time and attention) actively continue to overrepresent symptoms for secondary gain.

A recent study examined post-deployment symptoms in US Marines who were deployed to a combat zone and sustained either blast exposure or concussion compared to those with neither exposure nor concussion [33]. The authors found that, compared to Marines without blast exposure or concussion, that post-deployment symptoms were more severe in those with blast exposure and most severe if concussion had been sustained. The study also reported a greater likelihood of sustaining a concussion if the Marine had a history of prior concussions.

An interesting finding has also been described in relation to cognitive complaints after concussion in patients in the Veterans Affairs medical system after returning from deployment. Cognitive complaints are out of proportion to the findings on objective cognitive measures [34]. Awareness of symptoms may be affected by recall bias, increased sensitivity to symptoms, misattribution of symptoms, or emotional factors that may lead to perception of cognitive dysfunction despite normal objective measures [7, 17, 35]. Minimization of symptoms absolutely occurs, but it is the least common of these presentations despite popular discussion to the contrary [31].

Diagnosis

Diagnosis is based upon clinical history and physical exam. Currently, there are no accepted radiologic or laboratory tests to diagnose concussion [7, 9]. Imaging acutely with CT is helpful in evaluating for more severe injuries or immediately life-threatening problems associated with blast injury, but is not sensitive for the diagnosis of concussion. If there is a lesion seen on neuroimaging, the event is no longer considered a concussion/mTBI, but instead is graded as a moderate or severe brain injury [35]. MRI is a promising method of diagnosis and is more sensitive than CT in detecting parenchymal damage to the brain in TBI [20], but more research is needed in determining its utility for TBI. Standard MRI modalities may not be sensitive enough to detect injury sustained in a concussion/mTBI, and while newer modalities such as functional MRI and diffusion tensor imaging (DTI) appear to be more sensitive [36, 37], there are still questions about the clinical interpretation of these findings [36]. In a recent study of US service members who sustained a blast-related concussion in Iraq or Afghanistan, DTI was able to detect abnormalities in 18 of 63 patients with normal CT scans; however, while this is more sensitive, it still only detected abnormalities in 29% of patients with clinically determined concussion [21]. The authors concluded that while this may demonstrate some evidence of axonal injury in patients with blast-related concussion, the diagnosis of concussion remains clinical as the majority of the patients with concussion did not have a definite abnormality on DTI [21].

While there are some imaging findings suggestive of poor outcomes in severe TBI (such as bilateral brainstem lesions or posterior brainstem lesions), MRI is not predictive of outcome in moderate TBI and may not be predictive in all cases of severe TBI [19, 20]. As the imaging findings are far less conspicuous, if present at all, in concussion/mTBI, one would expect that interpretation of findings in mTBI would be more difficult and less predictive of outcome. Routine variation between normal individuals also complicates interpretation of findings in the setting of mTBI or concussion injuries evaluated by sensitive imaging techniques, given the enormous complexity of the brain and high variability between persons [38].

Documenting the details about the event is helpful in determining the level of injury severity (mild, moderate, or severe TBI) and may be helpful in the future to determine changes in treatment as more is discovered about concussion. It is also helpful in communicating the extent of the injury to other providers [9]. In the military setting, a commonly used test is the MACE. The MACE is helpful in that it creates a consistent framework for the evaluation of a patient suspected to have sustained a recent concussion and is fairly simple;

however, it has not been clinically validated [14]. In theater, much of the focus has been on the cognitive score, but it is the clinical history that is more important in making the diagnosis of concussion. Patients with an alteration of consciousness after a head injury should have at least one positive answer on the MACE clinical history portion. The cognitive score may serve as a measure of severity; however, in practice, it appears to be less helpful. A MACE cognitive score of less than 25 out of a possible 30 is considered abnormal and consistent with an injury. However, clinical experience in theater has shown that patients with a concussion by clinical criteria and postconcussive symptoms frequently score better than 25, and conversely some patients without a concussion score less than 25. A study using the MACE for soldiers in Iraq found that the MACE exam, if administered more than 12 h from the time of injury, was neither sensitive nor specific and was not clinically useful [37]. The MACE exam is helpful in providing consistency in evaluation, and the history portion should identify patients that meet clinical criteria for concussion (clinical history remains the standard for the diagnosis of concussion), but the conclusions one can make from the cognitive score are very limited.

Clinical criteria for concussion are inclusive and vary based on the source [37]. The US Department of Defense uses the definition of concussion proposed by the Mild Traumatic Brain Injury Section of the American Congress of Rehabilitation Medicine [13, 32] with the addition of a fifth criterion of the finding of the absence of an intracranial lesion on imaging (Box 2).

Box 2 The Department of Defense and Department of Veteran Affairs Traumatic Brain Injury Task Force Criteria for Mild TBI/Concussion

A traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event:

1. Any period of loss or decreased level of consciousness
2. Any loss of memory for events immediately before or after the injury
3. Any alteration of mental state at the time of the injury
4. Neurological deficits that may or may not be transient
5. Absence of intracranial lesion

In the setting of the theater of combat and blast-related concussion, generally patients are not returned to duty until they are symptom-free, regardless of whether there is an associated loss of consciousness associated with the concussion/mTBI. Loss of consciousness may have some utility as a descriptor of the event, creating a contextual framework when approaching the patient and managing expectations, and is sometimes used administratively in the military, but in clinical care, the presence or absence of loss of consciousness does not change management as patients are treated supportively until symptom resolution. While the mechanism is different, and patients are returned to full duty as opposed to returned to play in competitive sport, this is consistent with the Zurich Consensus Statement on Concussion in Sport, and the AAN position statement on sports concussion in October 2010, and AAN educational materials in 2014 which recommends that athletes do not return to play until symptom-free, remain symptom-free with provocative testing, and are evaluated by a neurologist or provider experienced in the treatment of concussion [22, 39, 40].

Diagnosis of concussion/mTBI based on clinical criteria is complicated because symptoms reported may be biased, forgotten, misattributed to concussion but caused by other factors, or confused with psychological symptoms that may not represent physical injury to the brain [2, 6–12, 17, 18]. While there are difficulties in making a diagnosis based on clinical history, as an observation by this author in treating patients both immediately in the deployed setting and after patients have returned from deployment, it appears that

patients in most cases are able to provide a detailed history of the event, despite concerns about memory issues in close relation to the event [6, 7]. It is best to obtain history as soon as possible, but in comparing experience with service members in Afghanistan and interviews with service members once they have returned home, most are able to provide a reliable history. Issues such as brief loss of consciousness versus post-traumatic amnesia with no loss of consciousness are difficult to determine in both settings, as is determining the duration of post-traumatic amnesia, but in most cases patients are able to provide a fairly reliable estimate that is generally consistent with the observations of their medics/corpsmen and medical providers as they are transported from point of injury to higher echelons of care. This observation has been consistent for neurologists both at NATO Role III Multi-National Medical Unit in Kandahar, Afghanistan, and the Craig Joint Theater Role III Hospital in Bagram, Afghanistan.

Treatment

The treatment of blast-related concussion is similar to that of concussion due to other mechanisms. The mainstay of treatment is rest and targeted treatment of clinical symptoms. Patients frequently report worsening of symptoms with exertion and appear to improve faster when allowed (or ordered) to rest, but supporting data overall are quite limited at this time. Gradual return to activity is encouraged [35]. Similar to findings in collegiate athletes after concussion, the period of recovery is variable for patients [41], even those exposed to the same explosive blast, so in general patients are followed until their symptoms remit or improve, then are returned to light activity before resuming full activity. Frequently provocative testing is performed before return to full activity to ensure there is not a relapse of symptoms with vigorous activity. Avoidance of reinjury while the patient is symptomatic and likely recovering from the injury is also important [13], and while second impact syndrome is controversial and generally seen in the pediatric population, it is conceivable a second concussion during a vulnerable period after a previous injury could have more concerning consequences [13, 35].

Education is also very important in the treatment of blast-related concussion, as concussion is very common, especially in young service members, who very frequently were (or are still) active in sports. It helps to explain that the concussion suffered as a result of a blast has a similar recovery pattern to any other concussion they or a friend may have had from a sports injury and that, in most cases, one would not expect long-term, persistent symptoms. There does not appear to be a significant difference in outcome between concussion caused by blast exposure and that caused by other mechanisms [5, 8, 11, 12, 17, 35]. It helps to create an expectation for full recovery [7, 16]. Discussion of the common symptoms may normalize the experience and reassure the patient. It may also be helpful to address the likelihood of other stressors contributing to symptoms, as in most cases the blast was both a physically and psychologically traumatic experience. Education may decrease the incidence of post-concussive symptoms at 6 months [16, 42]. In a review of several studies conducted in Finland, the Netherlands, Great Britain, New Zealand, the USA, and Canada which examined early interventions after concussion, it was consistently found that education about symptoms of post-concussive syndrome, reassurance, and reattribution of the symptoms to a benign cause (concussion) were effective in preventing long-term symptoms [42]. The terms “concussion,” “mild traumatic brain injury,” and “mTBI” are used interchangeably [6, 7, 13], but the diagnostic label and management of expectations are important [7, 17, 37, 43]. “Concussion” suggests an event that has occurred in the past, and a clinical state, whereas “mild traumatic brain injury” implies a pathological state [7, 13] that may be ongoing, or permanent “brain damage.” Many patients can identify with having a concussion and have a positive perception of their likely recovery. Fewer patients can identify with having a brain injury of any type and generally do not have positive expectations for recovery.

By observation, addressing somatic symptoms does appear to improve recovery. Treatment of symptoms in relation to blast-related concussion is no different than treatment of these symptoms from non-blast concussion or these symptoms in isolation. Headaches are quite common after a blast exposure and are frequently the factor that limits return to activity. It is ideal to take a detailed history of headache to determine if it is similar to a primary headache syndrome such as tension or migraine. Treatment of post-traumatic headache is no different than treating a primary headache syndrome. Most post-traumatic headaches have several features in common with migraine and tend to respond to migraine medications, including prophylactic medications such as tricyclic antidepressants and abortive medications such as nonsteroidal anti-inflammatory medications and triptans [18], although if there are features suggestive of a different headache syndrome, it may be helpful to change the treatment strategy accordingly. It is recommended that narcotics are avoided for treatment of post-concussive headaches [16, 18].

Sleep disturbances are very common after blast-related head injury, likely due to a combination of factors including environment, acute stress, and the injury itself. Frequently if the sleep disturbance is addressed, headaches and cognitive symptoms also improve. Sleep hygiene is the most important factor and, unfortunately, is one of the most difficult to address in the setting of ongoing combat operations. Rest in a quiet environment is key, along with avoidance of video games and energy drinks very commonly used by service members. Amitriptyline appears to be especially helpful in treating headache and sleep disorders after a blast-related concussion if pharmacological treatment is required, but other agents such as diphenhydramine, mirtazapine, melatonin, zolpidem, and temazepam have also been helpful for short-term treatment.

Tinnitus, hearing loss, and tympanic membrane rupture are very common after blast-related concussion. Tympanic membrane rupture generally will heal on its own. If there are concerns for infection, one can start a 7-day course of ciprofloxacin otic drops, but in most cases antibiotics are not needed. Patients should avoid getting water or foreign objects in the ear. If the tympanic membrane does not heal in 60–90 days, consider referral to an otolaryngologist for further evaluation. Hearing is also frequently impaired. Treatment is supportive, and in most cases, hearing improves. If not improved in 60–90 days, consider audiology evaluation. Unfortunately, there is no accepted treatment for tinnitus. Treatment of tinnitus is supportive.

Balance dysfunction frequently occurs in the acute setting after the blast. Immediately after the blast, patients frequently have difficulty maintaining their balance with running or walking, but often recover even with just brief rest. Recovery of vestibular function is generally very rapid, so it is uncommon for it to persist. With subjective complaints of dizziness, it is also very uncommon to find any deficits on a general neurological exam. Most patients appear to improve in 3–7 days, which is consistent with data from sports literature [41, 44].

Cognitive complaints generally improve with time. Treatment is supportive as there are limited data for pharmacological treatments after concussion. Most patients report resolution of cognitive symptoms within 1–2 weeks from the injury which appears consistent with data from sports literature [35, 41]. There also appears to be some subjective component to cognitive dysfunction that may be due to event recall bias, mood disorders, stress, or anxiety [45]. Subjective complaints of cognitive dysfunction also appear to be more prominent than those measured on formal neuropsychological testing, which is also consistent with the findings of subjective cognitive dysfunction in patients who have returned from deployment evaluated in the Veterans Affairs healthcare system [34].

Acute stress and mood disorders are very important contributors to continued symptoms after concussion [6, 7, 10, 17, 35, 43, 45]. Treatment of acute stress symptoms, PTSD, and mood disorders is no different in a patient with a history of concussion than one without a prior history. Referral to a combat stress provider, psychologist, or psychiatrist may be helpful if

symptoms are not well managed in the primary care setting. Early intervention to treat acute stress symptoms is recommended [10, 12].

Return to Duty

After a blast-related concussion in combat, it is important to determine when a patient is safe to return to duty. Similar to literature in sport-related concussion, service members exposed to blast or other mechanism of injury are generally not returned to duty unless symptom-free [22, 39]. There may be situations where the patient must return to duty due to a combat situation prior to resolution of symptoms, but this is very strongly avoided and uncommon. Service members are encouraged to rest by medics, corpsman, and/or primary care providers trained in the treatment of concussion, adhering to clinical practice guidelines for the treatment of concussion [14], and if symptoms persist or a patient has concerning findings, they are referred to specialty concussion center and/or a neurologist in the theater of operation for further evaluation or imaging. Patients are evaluated by the specialty provider as needed and referred for additional testing as indicated by clinical history or findings on exam. As determined by the theater neurologist or specialty provider, if indicated, patients may be additionally evaluated by a physical therapist for musculoskeletal complaints or balance issues in relation to the event, an occupational therapist to ensure the patient will be able to perform once returned to duty and tolerate the physical stresses associated with their duty, and a neuropsychologist or psychologist trained in cognitive testing if there are cognitive issues after the injury. Psychiatry, psychology, and combat stress providers may also be utilized in the treatment of patients with concussion when there is a significant component of acute stress reaction (ASR) or PTSD. Prior to return to duty, patients are tested with provocative testing to determine if symptoms return with exertion. Patients with persistent symptoms are instructed to rest, then gradually return to activity. Patients are not returned to full duty until they are symptom-free at baseline and do well on provocative testing, or have returned to their premorbid baseline (as in the case of patients with preexisting migraine or other symptoms that may appear similar to post-concussive symptoms) [14].

Outcomes

While the mechanism of injury in blast-related concussion is significantly different than non-blast-related concussion, outcomes after the injury, regardless of mechanism, appear to be similar [5, 8, 11, 12]. Patients with blast- and non-blast-related concussion had similar cognitive outcomes and symptomatic outcomes regardless of mechanism [5, 8, 11, 12]. There has not been a consistent association between blast mechanism and post-concussive symptoms [5, 12, 46]. In comparison to disability in blast- versus non-blast-related concussion in patients evacuated from theater for injury, there was not a significant difference in neuropsychological testing outcomes based on mechanism, but patients injured in theater by any mechanism did have worse outcomes and more prolonged symptoms than findings in studies with comparable civilian patients [30]. There may be several potential reasons for this difference, which are likely military- or deployment-specific. It also is important to consider that patients evacuated from theater for concussion are not likely representative of the majority of patients with concussion in the military. Most patients injured in theater did recover and were able to remain in theater, most often returning to full duty. Those evacuated did not typically have more objective differences on exam, but did typically have more reported symptoms, especially more psychological symptoms, than those who were not evacuated from theater.

Another finding in evacuated military personnel was that the control group with blast exposure but no concussion did significantly worse on neurobehavioral outcomes, psychiatric measures, and headache measures, despite similar performance on neuropsychological testing of controls. This is suggestive that other factors are likely involved in poor performance of patients exposed to blast

without concussion. The authors of this study suggest that increased combat exposure, subconcussive injury, or misclassification of injury (patients that were classified as not having concussion that may have had an unrecognized concussion) may play a role in this difference [30].

Post-concussive symptoms are more common in patients who are preoccupied with brain damage or have worsening of symptoms with exertion [16]. This reinforces the role of education in the treatment of concussion to improve perceptions and outcomes. Post-concussion symptoms may also be more common in women than in men, which has been seen in both in the civilian [47] and the military population [46]. While there are some theories as to why this observation occurs, the reasons for this are unclear and are especially difficult to understand given female animals used in experimental models of concussion appear to fare better than their male counterparts [47].

Compensation and litigation are frequently cited as risk factors for continued post-concussion symptoms or post-concussion syndrome (PCS) [7, 17, 35, 48]. Compensation does present a difficult problem in the military population. Forms of compensation, even if not consciously pursued, are a factor in patients with concussion sustained in combat. Those with continued symptoms are allowed to rest, often leave the combat area, and are sometimes awarded medals for the injury. Patients may also be eligible for monetary compensation for the injury when they leave the military. Those who recover rapidly or do not continue to report symptoms are not provided the same support even if they had participated in an equal or greater share of combat, deployment, hardships, or suffered the same or greater injury. There may be a sense of entitlement that one should also receive the same compensation as their comrades who do report symptoms, removing essentially any incentive for those injured to underreport symptoms or to report symptoms have resolved. There can be a perception of unfairness if one member is compensated for a comparable injury and another is not, simply based on continued report of symptoms. This issue is very apparent in the process of separating or retiring from the military. Any ongoing issues are encouraged to be reported by fellow service members and senior enlisted to ensure entitlements are secured. This process is not necessarily wrong because it is important to accurately care for and compensate those who have served and suffered injuries, but it may influence reporting of symptoms and discourage symptomatic improvement. This may be a military specific cultural factor contributing to ongoing symptoms that cannot be well measured, and there may be additional factors related to resilience and the culture that develops in injured service members separated from their unit. In a 2014 study of military personnel evacuated from theater for head injury, there was concern that unmeasured factors not related to severity of combat exposure, headache, PTSD, depression, or other measured factors considered in analyses of risk factors for outcomes after concussion may influence outcome. The authors suggest duty-related cognitive assessments and emotional intelligence testing should be explored as additional causes that may play a role in patients evacuated from theater with concussion injury [30].

Surprisingly, post-concussive symptoms are also not well associated with head injury or concussion and can occur in patients who have not had head injuries [5, 12, 17, 45, 46, 49]. Several investigations have found that post-concussive symptoms are much more closely associated with PTSD than with a history of concussion [6, 7, 10, 12, 17, 43]. The interaction between PTSD and post-concussive symptoms or TBI and PTSD is complicated, however. While it seems that TBI may not correlate well with post-concussive symptoms, a 2014 study of post-deployment Marines suggests TBI can be a predictor of PTSD. Data from the Marine Resiliency Study Team found TBI to be a strong predictor of PTSD symptoms after deployment, with near double the rate of post-deployment PTSD in Marines with little or no pre-deployment symptoms [29]. Risk of PTSD also increased with the severity of the TBI. The proposed mechanisms include injury to prefrontal cortical networks also implicated in PTSD leading to worsened recovery from stressful events, increased emotional impact of the injury, and TBI

occurring in a more emotionally traumatic setting that cannot be controlled for when accounting for overall combat exposure [29]. The overlap between PTSD and post-concussive symptoms makes determination of the underlying cause of symptoms difficult, and as they are commonly comorbid conditions, it is likely that each has influence on clinical outcome.

Despite the poor association between concussion and post-concussive symptoms, and complicated association between post-concussive symptoms and psychiatric comorbidity, there are some symptoms that may be more strongly related to concussion alone. Hoge and coauthors, in a 2008 study of US soldiers returning from Iraq, did find that concussion with loss of consciousness was associated with a higher risk of headache [6]. Blast-related concussion may have some additional associated symptoms as well. Wilk and coauthors [5] found that blast-induced concussion with loss of consciousness (but not without loss of consciousness) was more likely to be associated with tinnitus and headache at 3 and 6 months after deployment, and Belanger and coauthors [12] found hearing loss was associated with blast injury, but was otherwise not related to increased risk of physical post-concussion complaints. In fact, there was a significant inverse relationship between blast mechanism and cognitive complaints in the study [5]. This has not been entirely consistent between studies, but many studies show that blast exposure may have a higher associated risk of PTSD [8, 10–12]. PTSD was very prevalent at a rate of approximately 40% in the population of US soldiers returning from Iraq, evaluated in the Hoge study in 2008 [6].

This is also noted observationally in the deployed setting. The experience in Kandahar, Afghanistan, at the Role III Multinational Medical Unit, Neurology Clinic, consists of over 250 consecutive patients with concussion/mTBI evaluated from December 2010 to August 2011. The majority of patients evaluated in theater were exposed to primary blast without brain injury from other mechanisms, a second group of patients suffered from primary and combined non-blast injury (tertiary blast injuries such as blunt trauma related to the blast) which may have contributed to the injury. A smaller number of patients suffered from concussion due to other mechanisms, such as primary non-blast concussion from falls, sports, non-blast combat injuries, or vehicle accidents. This is in contrast to evaluations of service members evacuated from theater who most often had mixed blast and non-blast injury [30]. Of note, determining the contribution of quaternary blast injury does not appear to be possible. There are exposures to light/electromagnetic, acoustic, and thermal energy as well as toxic fumes with each blast, but the exposure varies considerably, even with patients exposed to the same explosive injury.

There does not appear to be a good dose–response relationship between blast exposure and persistent symptoms. It is not an infrequent occurrence that 2–6 service members will require treatment after a single blast. Service members involved in the same blast may report very different symptoms or duration of symptoms. Also, it is not uncommon that soldiers closer to the blast, some close enough to suffer fragmentation injuries, have less symptoms than those further from the blast and sometimes fewer post-concussive symptoms than patients who did not meet clinical criteria for concussion in the same blast. Between the two neurology providers in Kandahar Air Field in 2010–2011, the return to duty rate was between 93% and 97%, which also appears to be consistent with the sports literature in resolution of post-concussive symptoms [35, 41].

Overall, the different mechanism of injury and potentially different patterns of injury in the brain do not result in significantly different functional outcomes, and similar to other mechanisms of injury, most patients return to baseline within a month of the concussion [12].

Conclusion

Concussion due to blast wave exposure has been recognized as a source of potential injury to military service members and has been recognized as a significant problem since World War I. Military physicians historically faced many of the issues

that we also face today. Patients exposed to an explosive blast may have injury to the brain through several mechanisms, including the primary blast wave, secondary effects from projectiles causing blunt or penetrating trauma, tertiary effects from projection of the body from the blast, and quaternary effects due to other factors in the blast exposure. Limited conclusions can be made based largely on animal data and data from more severe brain injury, but there are likely microscopic changes that do occur in the brain parenchyma as a result of blast injury. These changes appear to improve with time, as do the clinical findings associated with blast-related concussion. The events and experience surrounding the blast exposure may also be important in pathology of concussion, as large studies have shown that PTSD and depression are important contributors to long-term symptoms. Several factors may contribute to symptoms after blast-related concussion, and it is likely that both physical and psychological components contribute to the overall clinical picture. Cultural factors in the military may affect recovery and perceptions of injury as well as reporting of symptoms. Perceptions of disability and expectations for recovery are important factors in recovery. While the mechanism of injury is different than concussion suffered in sports and other blunt trauma, clinical outcome is more closely associated with the severity of the injury rather than the mechanism of injury. Persistent symptoms are most likely associated with comorbid conditions or associated factors [17, 35], and the overall prognosis, with return to normal baseline function after concussion, is quite good. As with other mechanisms of concussion, treatment remains based upon clinical diagnosis of an injury, rest, education, and symptomatic therapy for somatic symptoms, such as headache, dizziness, and sleep disorders.

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Sleep/Wake Disturbances in Mild Traumatic Brain Injury Patients

Joseph Krainin, Aimee Alphonso Morrison, and Michael B. Russo

Introduction

Mild traumatic brain injury (mTBI) may disrupt both neuronal synaptic circuitry and glial myelin maintenance diffusely throughout the brain and brainstem. As mechanisms for initiating and maintaining sleep as well as initiating and maintaining *wake* are distributed throughout the brain and brainstem, damage to any brain or brainstem region is likely to impair some aspects of the intricate sleep/wake system network. TBI-related sleep/wake disorders – similar to sleep/wake disorders in general – may impair either or both nighttime sleep and daytime function. Insomnia, an inability to initiate and/or maintain sleep, is reported in up to 24% of the general population [1]. In the mTBI population, insomnia has been reported in up to 92% of patients [2]. Excessive daytime sleepiness (EDS), a severe impairment of daytime alertness, is reported in up to 20% of the general population [3], in part due to the over 85 sleep disorders identified by the American Academy of Sleep Medicine. In the mTBI population, EDS has been identified in up to 88% of patients. Prior to the onset or recognition of insomnia or EDS, subtle symptoms of sleep/wake disturbance may occur, including mild cognitive impairment, headaches and fatigue, appetite change, anhedonia, and mood instability. These commonly seen mTBI symptoms may be harbingers of incipient sleep/wake disturbances, or they may represent comorbid illnesses.

This chapter will discuss (1) the anatomy and physiology of the sleep/wake initiation and maintenance systems, (2) suggest mechanisms whereby mTBI may precipitate specific sleep disorders, (3) present illustrative case histories, and (4) discuss specific non-pharmacologic, pharmacologic, and experimental therapies.

Sleep/Wake Systems: Basic Anatomy and Physiology

The relationships among sleep, wake, and TBI may best be understood by thinking of sleep/wake centers and their projections as a distributed network within the brain and brainstem. TBI may cause subtle damage that disrupts a portion of that network. More severe injury may cause complete failure of a sleep/wake center. The signs and symptoms that result are related to the sleep/wake function of the area damaged and its projections. For example, if the lateral hypothalamus is damaged,

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the patient may have diminished release of hypocretin/orexin, the peptide that stabilizes the wake/sleep states. Magnetic resonance imaging (MRI) and functional MRI (fMRI) imaging of mTBI subjects versus healthy controls found an increased lesion burden and altered connectivity in mTBI patients compared with controls [4]. Severe damage to the lateral hypothalamus can result in narcolepsy, wherein a patient cannot effectively remain awake during the day nor can that patient effectively remain asleep during the night. The following sections describe the sleep/wake centers and projections so that the reader can better understand how even subtle traumatic damage can disrupt sleep/wake functions. Normal sleep is divided into non-rapid eye movement (NREM) and rapid eye movement (REM) sleep. The stages are wake (W), drowsy, N1 (non-REM sleep stage 1, equivalent to light sleep), N2 (non-REM sleep stage 2, equivalent to early slow-wave sleep), N3 (non-REM stages 3 and 4, equivalent to deep sleep), and REM sleep; sleep is an active process that cycles at an ultradian rhythm (a biological cycle occurring within a 24-hour period) of about 90 minutes. Stage N1 is considered a transition between wake and sleep. It occurs upon falling asleep and during brief arousal periods and usually accounts for 5–10% of total sleep time. Stage N2 occurs throughout the sleep period and represents 40–50% of total sleep time. Stage N3 is classically referred to as "delta wave sleep" and occurs mostly in the first third of the night.

Upon falling asleep, waking usually transitions into NREM sleep stages N1 quickly followed by N2. REM follows NREM sleep by about 90 minutes and occurs 4–5 times during a normal 8- to 9-hour sleep period. The first REM period of the night may be less than 10 minutes in duration, while the last may exceed 60 minutes. Awakening after a full night's sleep is often from REM sleep. In adults, sleep of 8–8.4 hours is considered fully restorative for most healthy young adults. In some cultures, total sleep often is divided into an overnight sleep period of 6–7 hours and a midafternoon nap of 1–2 hours.

Sleep is a state of unconsciousness in which the brain is relatively more responsive to internal than to external stimuli. The predictable cycling of sleep and the reversal of relative external unresponsiveness are features that assist in distinguishing sleep from other states of unconsciousness. The brain gradually becomes less responsive to visual, auditory, and other environmental stimuli during the transition from wake to sleep, which is considered by some to be stage N1 of sleep.

Historically, sleep was thought to be a passive state that was initiated through withdrawal of sensory input. Currently, withdrawal of sensory awareness is believed to be a factor in sleep, but an active initiation mechanism that facilitates brain withdrawal also is recognized.

NREM sleep is controlled by complex initiating and maintenance mechanisms, the extent of which is not fully elaborated. Probably no single sleep-generating center exists. A more likely mechanism is sleep-generating circuits with inputs from brainstem and hypothalamic neuronal groups. Within these circuits, sleep initiation may begin with the emergence of inhibitory signals from the anterior hypothalamic preoptic nucleus directed caudally toward the brainstem reticular core and posterior hypothalamus. The preoptic nucleus inhibits the histaminergic posterior hypothalamic tuberoinfundibular region through gamma-aminobutyric acid (GABA) and probably acetylcholine [5].

The tuberoinfundibular region projects rostrally to the intralaminar nuclei of the thalamus and to the cerebral cortex. Inhibition of the tuberoinfundibular region is a critical step toward falling asleep because it results in functional disconnection between the brainstem and the more rostral thalamus and cortex. A decrease in ascending thalamic cholinergic transmissions occurs in association with decreasing cortical responsiveness. In addition to inhibiting higher cortical consciousness, the tuberoinfundibular tract projects caudally into the pontine reticular system and inhibits afferent transmissions from ascending cholinergic tracts.

NREM is an active state that is maintained partly through oscillations between the thalamus and the cortex. The three major oscillation systems are sleep spindles, delta oscillations, and slow cortical oscillations. Sleep spindles, a hallmark of stage N2 sleep, are generated by bursts of hyperpolarizing GABAnergic thalamic reticular

neurons. These bursts inhibit thalamocortical projection neurons. As deafferentation spreads, corticothalamic projections back to the thalamus synchronize. As hyperpolarization of the thalamic reticular neurons progresses, delta waves are produced by interactions from both thalamic reticular and cortical pyramidal sources. Slow cortical oscillations are produced in neocortical networks by cyclic hyperpolarizations and depolarizations.

REM sleep is generated by mesencephalic and pontine cholinergic neurons; hence, these are referred to as REM-on neurons. As REM sleep initiates, monoaminergic locus coeruleus and serotonergic raphe neurons become inactive and are, thereby, referred to as REM-off neurons.

REM is characterized by muscle atonia, cortical activation, low-voltage synchronization of the electroencephalogram (EEG), and rapid eye movements. REM may be considered to have both tonic and phasic characteristics. Tonic muscle atonia is present throughout REM sleep. It results from inhibition of alpha motor neurons by clusters of peri-locus coeruleus neurons, which are referred to collectively as the dorsolateral small cell reticular group.

Projection of the presumed cholinergic dorsolateral small cell reticular group is through the medullary reticular formation, which projects through the ventrolateral reticulospinal tract to inhibitory spinal and bulbar interneurons. Glycinergic interneurons produce postsynaptic inhibition and hyperpolarization of the spinal alpha motor neurons. Tonic cortical activation with EEG desynchronization is promoted by projections from cholinergic lateral dorsal tegmental and pedunculopontine tegmental neurons to the thalamic nuclei. Other projections through brainstem reticular formation neurons are likely to be involved as well.

Phasic rapid eye movements are composed of lateral saccades generated in the paramedian pontine reticular formation and vertical saccades thought to be generated in the mesencephalic reticular formation. REM density is a term used to describe the frequency per minute of the eye movement bursts.

Phasic pontine-geniculate-occipital (PGO) spikes are another neurophysiological feature of REM sleep. These spikes appear to be generated by lateral dorsal tegmental and pedunculopontine tegmental neuronal bursts. They are projected to the lateral geniculate and other thalamic nuclei and then to the occipital cortex. PGO bursts precede rapid eye movements by several seconds. Increases in PGO bursts are seen after REM sleep deprivation. Other phasic features of REM sleep include periodic skeletal muscle twitches, increased heart rate variability, pupil dilation, and increased respiratory rate.

Circadian sleep rhythm is one of the several intrinsic body rhythms modulated by the hypothalamus. The suprachiasmatic nucleus sets the body clock to approximately 25 hours, with both light exposure and schedule cues entraining to the 24-hour cycle. The retinohypothalamic tract allows light cues to directly influence the suprachiasmatic nucleus. Light is called a "zeitgeber," a German word meaning "time-giver," because it sets the suprachiasmatic clock. The nadir of the circadian sleep rhythm is in the early morning. The downswing in circadian rhythm prior to the nadir is thought to assist the brain in remaining asleep overnight for full restoration by preventing premature awakening. The morning upswing then facilitates awakening and through the day acts as a counterbalance to the progressive discharge of awake neuronal activity. After the circadian apex in the early evening, the downswing aids sleep initiation. This model explains the relatively steady cognitive function throughout wakefulness.

Body temperature cycles are ultradian rhythms also under hypothalamic control. An increase in body temperature is seen during the course of the day and a decrease is observed during the night. The temperature peaks and troughs are thought to mirror the sleep rhythm. People who are alert late in the evening (i.e., evening types) have body temperature peaks late in the evening, while those who find themselves most alert early in the morning (i.e., morning types) have body temperature peaks early in the morning.

Melatonin has been implicated as a modulator of light entrainment. It is secreted maximally during the night by the pineal gland. Wake is promoted by monoaminergic neurons (dopamine and serotonin), by acetylcholine, and stabilized by orexin/hypocretin.

In the 1920s, von Economo [6] identified neural regions responsible for hypersomnia, narcolepsy,

and insomnia by studying the brains of his patients. In the 1940s, Moruzzi and Magoun [7] discovered during experiments with cat brains that ascending stimulation resulted in an EEG pattern similar to the wake state, while in the absence of stimulation, the EEG pattern resembled an unconscious state. The ascending reticular activating system described by them in 1949 was a discovery that led to the realization that the waking state was an active process driven by sensory stimulation channeled through dorsal spinal and brainstem tracts. Disruption of these tracts would lead to hypersomnolence.

Sleep and Traumatic Brain Injury (TBI)

In an early study of the relationships between sleep and TBI, Cohen and coauthors [8] found in a study of motor vehicle accident patients in Tel Aviv Israel:

- 73% of patients hospitalized with TBI complained of sleep problems
- 82% of the sleep problems were insomnia (initiating, maintaining sleep)
- 73% complained of excessive daytime somnolence

Cohen [8] was the first to recommend that *early evaluation and treatment of sleep disturbances (in TBI patients) must be considered an integral part of the rehabilitation process.* Although his recommendations were not widely appreciated at the time, his continued research has made them more widely accepted.

TBI Fragments Sleep and Results in Sleep Deprivation-Related Effects

TBI may impair judgment, concentration, working memory, and other prefrontal-mediated tasks through direct damage to the prefrontal regions and/or through sleep deprivation-related comorbid impairment. In a review of the sleep changes following several types of brain injuries, George and coauthors [9] and Ron and coauthors [10] showed in acute brain injury (less than 2 weeks) an increase in sleep-onset latency, an increase in light sleep, and an increase in awakenings after sleep onset (wake after sleep onset, WASO). These increases in sleep fragmentation were counterbalanced by decreases in REM sleep and decreases in slow-wave sleep. After 2 weeks, in the subacute stage, the investigators noted a reversal of the earlier described architectural pathologies and noted improvement toward normal sleep architecture. They hypothesized that tracking sleep architecture could provide a prognostic tool.

In tasks requiring judgment, increasingly risky behaviors emerge as the total sleep duration is limited to 5 hours per night [11]. The high cost of an action seemingly is ignored as the sleep-deprived individual focuses on limited benefit. A potential explanation for decreasing performance in sleep-deprived mTBI patients is the occurrence of microsleep. Microsleep is defined as brief (several seconds) runs of theta or delta activities that break through the otherwise beta or alpha EEG of waking. It has been seen to increase with sleep deprivation. In studies in which polysomnography is recorded simultaneously, microsleep impairs continuity of cognitive function and occurs prior to performance failure [12–15]. In TBI patients who present with new onset blackout episodes, lasting minutes or longer, and not associated with convulsive movements, sleep intrusions are an important consideration. These patients may not recognize how sleepy they are and may fall asleep driving and in other equally inappropriate situations. These patients will always complain of severe sleepiness when questioned.

Sleep deprivation is a relative concept. Small amounts of sleep loss (e.g., 1 hour per night over many nights) have subtle cognitive costs, which appear to go unrecognized by the individual experiencing the sleep loss. More severe restriction of sleep for a week leads to profound cognitive deficits similar to those seen in some stroke patients, which also appear to go unrecognized by the individual.

Subjective Measures of Sleepiness

Stanford Sleepiness Scale [16]

The Stanford Sleepiness Scale is a subjective scale to assess the degree of sleepiness at the moment of testing. The patient is presented with seven statements and selects the one that best represents his/her current feelings. This test may be used to assess a patient's sleepiness level at the time of the visit and compare sleepiness from visit to visit. One example of how the Stanford Sleepiness Scale may be applied is shown in Fig. 1.

Epworth Sleepiness Scale [17]

The Epworth Sleepiness Scale (Fig. 2) is a subjective measure that operationalizes sleepiness by asking how likely the individual is to fall asleep in specific, well-known situations. The

STANFORD SLEEPINESS SCALE

An Introspective Measure of Sleepiness

Please select the statement that reflects how alert you feel at the moment

Degree of Sleepiness	Scale Rating
Feeling active, vital, alert, or wide awake	1
Functioning at high levels, but not at peak; able to concentrate	2
Awake, but relaxed; responsive but not fully alert	3
Somewhat foggy, let down	4
Foggy; losing interest in remaining awake; slowed down	5
Sleepy, woozy, fighting sleep; prefer to lie down	6
No longer fighting sleep, sleep onset soon; having dream-like thoughts	7

Fig. 1 The Stanford Sleepiness Scale (SSS). The SSS rating subjectively assesses how sleepy an individual is at the time of the assessment by asking the stage of alertness with which they would characterize his or her mood. A scale rating below 3 (3–7) indicates a significant sleep debt. (Data from Hoddes et al. [16])

THE EPWORTH SLEEPINESS SCALE

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life *in the recent past.* Even if you have not done some of these things recently try to work out how they would have affected you. Use the following scale to choose *the most appropriate number for each situation:*

0 = no chance of dozing
1 = slight chance of dozing
2 = moderate chance of dozing
3 = high chance of dozing

Situation	Chance of Dozing
Sitting and reading	_____
Watching TV	_____
Sitting inactive in a public place (e.g. a theater or a meeting)	_____
As a passenger in a car for an hour without a break	_____
Lying down to rest in the afternoon when circumstances permit	_____
Sitting and talking to someone	_____
Sitting quietly after a lunch without alcohol	_____
In a car, while stopped for a few minutes in traffic	_____
Total Score	_____

Fig. 2 The Epworth Sleepiness Scale (ESS). The ESS subjectively assesses how sleepy an individual has been over the past month by asking how likely he or she is to fall asleep in eight common situations. The scores across the eight situations are summed to obtain the ESS score, with 0 being the lowest score and 24 the highest. Healthy, well-rested adults have Epworth scores in the 2–10 range. Idiopathic hypersomnia, narcolepsy, and obstructive sleep apnea patients have scores up to 23 and 24. The ESS score distinguishes individual and diagnostic groups over a wide range of daytime sleepiness. (Used with permission of Oxford University Press from Johns [17])

Epworth Scale reflects the patient's self-assessment of sleepiness over the prior several days, weeks, or months and is the most widely used instrument to measure subjective sleepiness in clinical practice. The Epworth Scale may be applied as shown in Fig. 2. Summation of the scores for all situations provides a global score. Global score ranges between 0 and 24. A total score of ≥10 is considered abnormal.

The Pittsburg Sleep Quality Index (PSQI) [18]

The PSQI (Fig. 3) assesses a larger range of sleep/wake symptoms and provides a more structured and detailed history of the wake/sleep problems. The results enable the clinician to better focus a differential diagnosis. The PSQI asks for input by the bed partner or roommate, and, therefore, is of decreased value in individuals who sleep alone.

The Fatigue Severity Scale [19]

The Fatigue Severity Scale is a validated tool for quantifying fatigue. A score of 4 or higher is considered abnormally high. This scale, when incorporated into the patient intake process, may increase sensitivity for identifying mTBI patients with daytime sleepiness. It contains nine statements that rate the severity of fatigue symptoms. The patient is asked to circle a number from 1 to 7, based on how accurately it reflects their condition and the extent to which they agree or disagree that the statement as it applies to them. Fatigue is distinct from sleepiness with fatigue best characterized by "lack of energy" and sleepiness as "the tendency to doze or towards falling asleep inappropriately." Some research suggests that women may have the tendency to complain of daytime dysfunction related to sleep disorders as fatigue more than men [20].

Objective Measures of Sleepiness/Wakefulness

Multiple Sleep Latency Test (MSLT) [21, 22]

The Multiple Sleep Latency Test is an objective measure of sleepiness performed the day following an adequate all-night polysomnogram. In order for an MSLT to be valid, it should be preceded by an overnight polysomnogram with at least 6 hours of sleep and not diagnostic for another primary sleep disorder, such as sleep

Pittsburgh Sleep Quality Index (PSQI)

- The Pittsburgh Sleep Quality Index (PSQI) measures sleep quality over the previous month and discriminates between good and poor sleepers.
- 19 self-rated questions; 5 multiple-choice questions rated by a bed partner or roommate
- Seven component scores each range from 0 (no difficulty) to 3 (severe difficulty):
  1. Subjective Sleep Quality
  2. Sleep Onset Latency
  3. Sleep Duration
  4. Habitual Sleep Efficiency
  5. Sleep Disturbances
  6. Sleeping medications use
  7. Daytime dysfunction
- Global score range of 0–21.
- Global score > 5 = significant sleep disturbance.

Advantage: *Larger range of pathologic; component scores: more specific and more sensitive assessments of both sleep and waking dysfunction.*

Fig. 3 The Pittsburgh Sleep Quality Index. (Data from: Buysse et al. [18])

apnea or periodic limb movement disorder (PLMD). Mounting evidence [23] suggests that actigraphy for at least 1 week preceding an MSLT is useful in ruling out insufficient sleep as the cause of excessive daytime sleepiness. Four to five nap opportunities (depending on the protocol) of 20 minutes each are provided during the MSLT. At each opportunity in a darkened room, the patient is instructed to let sleep occur. Sleep latency is the length in minutes from lights-off to any stage of sleep, measured by standard polysomnographic methods. A sleep-onset REM period (SOREMP) is defined as the occurrence of REM sleep within 15 minutes of sleep onset. Excessive daytime sleepiness is defined as a mean sleep latency (MSL) of ≤8 minutes. MSLT diagnostic criteria for idiopathic hypersomnia are MSL ≤8 minutes and ≤1 SOREMP; a pathological MSL and ≥2 SOREMPS is supportive of a diagnosis of narcolepsy with cataplexy (also referred to as narcolepsy type 2 in the *International Classification of Sleep Disorders*, Third Edition [ICSD-3] [24]).

Maintenance of Wakefulness Test (MWT) [25]

The Maintenance of Wakefulness Test is an objective measure of wakefulness performed the day following an adequate all-night polysomnogram. The patient is provided 5 stay-awake opportunities of up to 40 minutes each. In a darkened room, while in a semi-reclining position, the patient is instructed to attempt to remain awake. Sleep latency is the length in minutes from lights-out to any stage of sleep, measured by standard polysomnographic methods. Mild sleepiness is scored as a sleep latency of between 10 and 15 minutes, moderate sleepiness is a sleep latency of 5–10 minutes, and severe sleepiness is a latency of less than 5 minutes.

Case Studies

Case 1: The Auto Accident

Patient History, Symptoms, Exams, and Studies

- A 49-year-old man complains of weight loss and slowly evolving weakness for 10–15 years.
- After multiple negative workups, patient referred to neurology.
- *When asked*, reported sleep-onset insomnia with daytime irritability but without excessive daytime sleepiness.
- MVA in 1985 went head first through windshield. Had brief loss of consciousness (LOC) with rapid return to full alertness and orientation. GCS 15. CT head normal.
- Exam: Emaciated. Hyperreflexia. Muscles atrophied; no fasciculations.
- MRI imaging findings (Fig. 4).

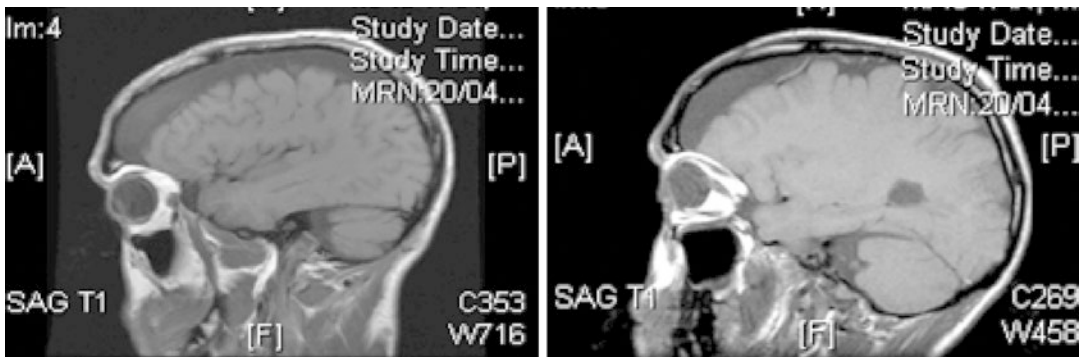

Fig. 4 Sagittal MRI shows large subdural hygromas bilaterally. Hypothesized etiology is that slowly evolving subdural hematomas formed following the 1985 injury. These subdural hematomas depressed motor regions causing sclerosis bilaterally of the primary motor regions. The hematomas eventually evolved to become hygromas

Take-Home Points

Glasgow Coma Scale (GCS) score may not reflect degree of injury. Early neuroimaging may not show lesions. Sleep problems may not be spontaneously mentioned, so provider must ask!

Case 2: The Football Player

Patient History and Symptoms

- A 39-year-old active duty soldier referred for intractable headaches.
- Constant headache after most recent injury (November 2008) when he used head as a battering ram during football game. Brief LOC, not hospitalized.
- Six concussions over 10 years, three without LOC, three with brief LOC. No nausea, vomiting, or seizures.
- *When asked,* complained of difficulty sleeping for 1 year.
- Denies memory/concentration impairments.
- Admits to neck pain and occasional tingling sensation in hands.

Headaches

Five-year history, right-sided hemicranial stabbing pain, radiating into posterior neck; moderate to severe intensity.

- All day, every day since recent injury.
- Denies nausea, vomiting, photo/phonophobia, exercise intolerance.
- Denies improvement with Imitrex or Excedrin® (GlaxoSmithKline, Brentford, UK).

Sleep

Difficulty falling asleep noticed since most recent injury with feeling of "mind racing." *Snores* loudly and awakens self. *Thrashes and jumps* and moves during sleep. Feels *sleepy and fatigued upon awakening* and during days. *Naps* once or twice per day.

Neurological Exam

Non-focal.

Imaging

Normal head CT.

Differential Diagnosis

- *Headaches:* primary vs. secondary? Atypical migraine, neuralgia, musculoskeletal, cervical spine origin?
- *Insomnia*: sleep-onset insomnia, possibly psychophysiological (a type of sleep-onset insomnia that results from excessive and chronic worry prior to sleep. The patient describes his/her mind as not turning off, or "racing" with thoughts that preclude relaxation and sleep onset. As the condition becomes chronic, the patient may begin worrying about whether he/she will be able to fall asleep, further contributing to the escalation of anxiety).
- *Obstructive sleep apnea*?
- *REM sleep behavioral disorder*, *periodic limb movements, restless legs, seizures*?
- *Daytime sleepiness:* secondary hypersomnia, sleep deprivation, post-traumatic narcolepsy, post-traumatic encephalopathy (early dementia pugilistica)?

TBI Type: Based Upon Available Info

- + LOC (brief)
- GCS – unknown
- Hospitalization – none
- Neurological examination – normal
- CT scan of the brain – normal

This leads us toward a determination of mild TBI.

Overnight Polysomnography

AHI 34 with desaturation episodes to 88%. (AHI is the *Apnea Hypopnea Index*). It represents the number of breathing interruptions per hour. Obstructive sleep apnea is defined as mild with an AHI of 5–15, moderate with an AHI of 16–30, and severe with an AHI >30. Venous blood desaturation is routinely measured during polysomnography by an infrared oximeter placed onto a finger. Normal awake venous blood oxygen saturations are usually considered normal when above 95% at sea level. Oxygen saturation <90% is considered abnormal.

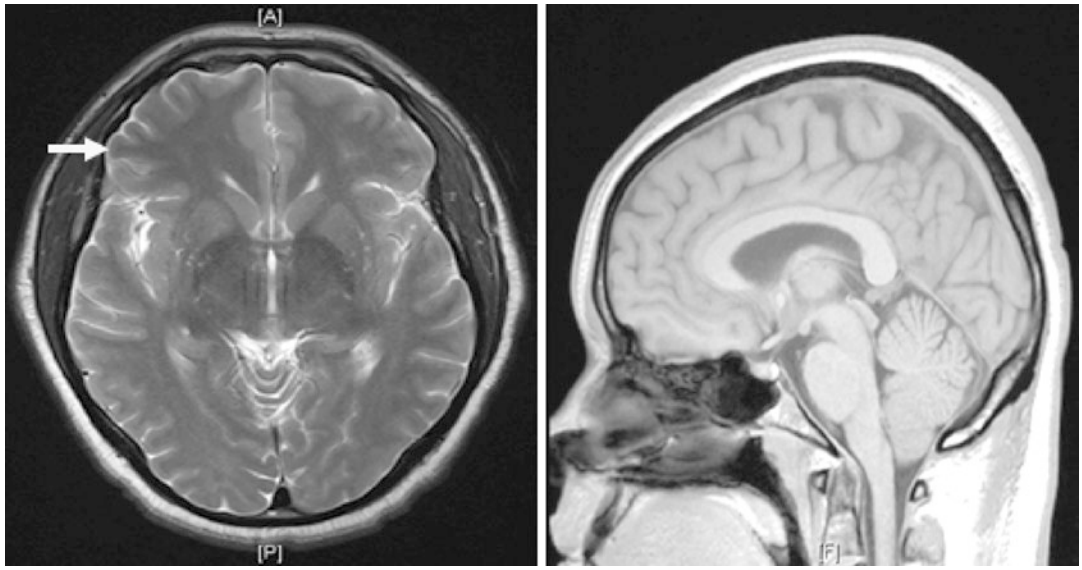

Fig. 5 On MRI, small white matter lesions are found in the right frontal area (left) and in the paramedian pons (right). These subtle macroscopic lesions most likely are the "tip of the iceberg" with significant microscopic damage disrupting the sleep/wake network

- MSLT shows sleep-onset latency of 6 minutes. No Sleep-onset REMs.
- MRI brain: white matter lesions in paramedian pons and right frontal regions (Fig. 5).

Diagnoses

1. Moderate TBI due to the MRI findings.
2. Post-traumatic obstructive sleep apnea due to the AHI of 34.
3. Sleep deprivation-related daytime sleepiness due to the poor sleep at night.
4. Insomnia: TBI-related psychophysiologic-type at sleep onset.

This patient has post-traumatic OSA, sleep deprivation-related excessive daytime sleepiness, and psychophysiological insomnia. The etiology of the OSA may include traumatic disruption of the anatomy through the pons, medulla, or upper cervical spinal cord.

These brainstem respiratory nuclear groups form a network that ensures reciprocal activation and inhibition of the respiratory cycle muscles: Pons, respiratory-modulated cells signal the medullary rhythm and pattern generator cells; medulla (upper), Botzinger cell groups pace respiration and signal descending inspiratory and expiratory pathways; and medulla (lower), major respiratory pump muscles nuclear clusters control diaphragm and intercostals.

Take-Home Points

More than one type of sleep disorder may be diagnosed in an individual. Lesions may be found on MRI that are not visualized on CT. Sleep problems may not be spontaneously mentioned, so provider must ask!

Case 3: The Boxer

Patient History, Symptoms, Exams, and Studies

- A 19 year-old military boxer complained of inability to sleep at night.
  - Five concussions, several with LOC. Other less severe head injuries.
  - Has irresistible urge to sleep during days and naps at work and before dinner.
  - Has frequent nighttime awakenings for no particular reason.
  - Vivid dreams, sometimes during daytime naps.

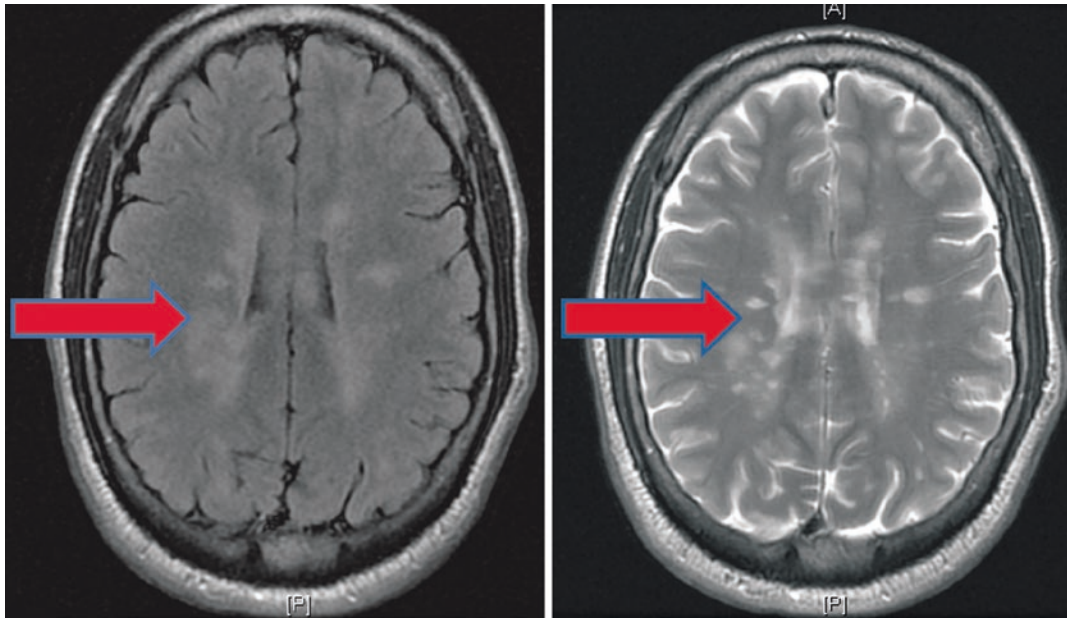

Fig. 6 On MRI, white matter lesions are found throughout the left and right hemispheres and throughout the brain stem. These lesions resemble those seen in multiple sclerosis (MS). The lab evaluation for MS did not show oligoclonal bands. If deterioration continues, and the clinical definition of lesions in time and space is met, then the patient would also be given a diagnosis of MS.

- Neuro exam positive: nystagmus, hyperreflexic, + Hoffman's and clonus, tremor
- CT brain: normal
- MRI brain: multiple lesions throughout brain and brain stem (Fig. 6)

Differential Diagnoses

- TBI: moderate
- Motor systems damage
  - Corticospinal tracts, basal ganglia (hyperreflexia and tremor)?
- Wake/sleep systems damage
  - Hypothalamus and basal forebrain (sleepiness)?
  - Brainstem, midbrain, and pontine damage: medial longitudinal fasciculus and ascending reticular activating systems (nystagmus)
- Overnight polysomnography:
  - No apnea/hypopnea
  - Frequent arousals
- Multiple sleep latency test
  - Sleep-onset latency of 5 min
  - 3 sleep-onset REMs

Diagnosis

Post-traumatic narcolepsy. Clinical findings of sleep intrusions during day and hypnagogic (upon falling asleep) and hypnopompic (upon awakening) hallucinations, confirmed by MSLT. In narcolepsy, cataplexy may or may not be present. Sleep paralysis is common but may not always be present. Suspected multiple sclerosis (MS), possibly post-traumatic in origin.

This patient developed post-traumatic narcolepsy, hypothetically through disruption of the hypocretin/orexin systems. Narcolepsy results when hypocretin/orexin neurons in the lateral hypothalamus fail to produce enough hypocretin/orexin neuropeptide to stabilize the wake and sleep states. If the diagnosis of narcolepsy with cataplexy (renamed narcolepsy type 1 in ICSD-3) is in question, laboratory testing for CSF hypocretin is now available and may help to clarify the diagnosis. Hypocretin values <110 pg/mL are highly specific for narcolepsy with cataplexy. The patient presents with sudden and inappropriate sleep onsets. The sleep is restorative, and upon

awakening the patient feels refreshed. During the night, the patient cannot sustain the sleep state and awakens frequently. Other manifestations are the occurrence of early onset REM periods, often within 30 minutes of sleep onset. These early REM periods may also occur when the patient is falling asleep and appear to the patient as vivid hypnagogic hallucinations. When cataplexy is present, the normal atonia seen in REM sleep is disrupted and is seen occurring inappropriately during the waking state. In response to sudden and strong emotion, most often spontaneous laughter, the patient with cataplexy may lose muscle tone. The loss may be mild, with jaw and abdomen muscles relaxing, or may be more severe, with hip and lower limb muscles relaxing. When the lower limbs are severely affected, the patient may fall to the ground, remaining conscious and alert. Cataplexy may develop if the atonia control network in the brainstem is disrupted. Tonic muscle atonia results from inhibition of alpha motor neurons by clusters of peri-locus coeruleus neurons referred to as the dorsolateral small cell reticular group. Projection of this presumed cholinergic small cell reticular group is through the medullary reticular formation, which projects caudally through the ventrolateral reticulospinal tract to inhibitory spinal and bulbar interneurons. Glycinergic interneurons produce postsynaptic inhibition and hyperpolarization of the spinal alpha motor neurons, hence the REM atonia. This circuit may be damaged in mTBI leading to muscle atonia at inappropriate times.

Take-Home Point

Impairment may begin insidiously. Ask about sleep and daytime function.

Classification and Treatment of Sleep Disorders in TBI Patients

Excessive Daytime Sleepiness (EDS)

EDS is one of the primary complaints reported by mTBI patients [26]. EDS may be defined as sleepiness or unintentional sleep episodes occurring at undesirable or inappropriate times and locations. EDS may be associated with severe and moderate sleep deprivation. With sleep deprivation-associated sleepiness, sleep refreshes, and adequate sleep satiates.

Excessive sleepiness also may occur with apparently ample sleep, such as in the idiopathic and recurrent hypersomnias or in long sleepers deprived of adequate sleep time. In the hypersomnias, sleep is not refreshing, and no amount of sleep satiates. TBI may cause hypersomnia in isolation or as part of a chronic traumatic encephalopathy syndrome.

Mild chronic sleep deprivation may have effects apart from excessive sleepiness. Some patients report attentional difficulties, loss of short-term memory or working memory problems, language difficulties, poor judgment and "unprofessionalism," irritability, moodiness, and confusion. Some of this may be described as feelings of disinhibition. Patients express that they feel tired and perform poorly, but they often deny feeling that they are about to fall asleep. Note that most patients seen for sleep deprivation-related complaints in clinical settings will be manifesting the effects of *chronic partial* sleep deprivation. Many of the symptoms of sleep deprivation overlap the symptoms of TBI. Treating the sleep deprivation will help resolve those symptoms due to poor sleep and distinguish those symptoms due to TBI.

Symptom Checklist

TBI patients report varying degrees of exhaustion, fatigue, and lack of physical energy. These common symptoms may be due to depression, anxiety, or chronic headache. As sleep disorders occur frequently in TBI patients, these symptoms must also be appreciated as potentially due to sleep deprivation-related EDS. Exhaustion and fatigue affect our emotional moods and potentially may cause pessimism, sadness, stress, and anger. In some depressed patients, sleep deprivation can improve their mood and affect. Complaints of poor sleep and daytime drowsiness predominate. Some patients complain of

clumsiness, incoordination, and weakness, while others complain of loss of energy, apathy, and feeling cold. Aldrich [27] listed the following signs of drowsiness: eye rubbing, decreased blinking rate, glazed and unfocused eyes, slow eye movements, heavy eyelids with drooping, closed eyes, fidgeting, yawning, slumped posture, reduced activity, slack facies, head-nodding, and sleep-seeking behavior. With mild and moderate chronic sleep deprivation of between 4 and 6 hours sleep per night, patients may report easy distractibility, tangentialism, short-term or working memory problems, word-finding difficulties, diminished judgment, increased risk-taking behaviors, increased irritability, increased moodiness, and indecisiveness.

Cognitive Behavioral Therapy and Sleep Hygiene

The first step toward improving sleep should always be a review of sleep hygiene behaviors, followed by cognitive behavioral therapy (CBT). Behavioral modification should include the following standard recommendations:

1. Associate the bed with sleep. Advise patients to avoid watching TV, eating, and evoking perturbing emotions in bed. The bed should be used for sleep (and sex) only. Associating the bed with activities other than sleep (including sex) can prolong sleep latency.
2. Advise patients to minimize noise, light, and temperature extremes during sleep with ear plugs, window blinds, warm blankets, or air conditioning. White noise, natural sounds, such as a gurgling brook, or nonvocal music may be helpful.
3. Advise patients with concerns of nocturia to avoid fluids after 8 p.m. This may reduce awakenings due to the urge to urinate.
4. A nap during the postprandial midafternoon circadian trough may not interfere with nighttime sleep and will improve alertness and performance. Short naps should be brief enough to avoid entering slow-wave sleep. Awakening from slow-wave sleep is more difficult, and sleep inertia effects may impair immediate post-awakening performance. If a longer nap is desired, awakening may be timed to occur from REM.
5. Advise patients to avoid exposure to bright light if they need to get up at night. Recommend small night-lights to illuminate likely pathways.
6. Nicotine should be avoided, particularly near bedtime and upon night awakenings.
7. Caffeine should be discontinued at least 4–6 hours before bedtime. Warn the patient of potential withdrawal effects if caffeine dependency exists.
8. Advise patients not to consume alcohol as a sleeping aid and to avoid excessive alcohol in the several hours prior to bed. Although alcohol is a depressant and may help induce sleep, the subsequent metabolism causes a sleep fragmenting withdrawal syndrome. This withdrawal may cause awakenings and may be associated with nightmares and diaphoresis.
9. A light snack prior to sleep may help prevent hunger from awakening some patients. Too heavy a meal close to bedtime may interfere with sleep.
10. Advise patients that vigorous exercise may arouse them and within 2 or 3 hours of bedtime may interfere with sleep induction. Advise that exercise is best scheduled in the morning or afternoon.
11. Advise patients to engage in a regular exercise routine. Healthy individuals who ran or walked 40 minutes, 3 days a week, experienced longer periods of deep sleep than less active individuals [28–31]. The net benefit of exercise on sleep has been shown to outweigh its potential drawbacks, even if close to bedtime [32].
12. Advise your patients to not sleep with their pets. Canine and feline wake/sleep hours differ from those of humans, and animal movements can awaken light sleepers.
13. Advise patients to try to establish and maintain the same bedtime every night and wake up at the same time every morning.

14. Advise patients to reduce evening stress by engaging in a relaxing ritual. For example, recommend the patient take a hot bath or shower, perform stretching or meditation, or listen to quiet relaxing music. The stress reduction routine may be repeated each evening to prepare the patient for sleep induction.
15. Advise a patient to keep a sleep diary. Adjustments to bedtime and wake up may be recorded in the diary. For example, recording incrementally earlier bedtimes for delayed sleep phase patients may re-enforce their improved sleep hygiene.

Recently, several internal-based CBT-Insomnia (CBT-I) platforms have become commercially available. These options may serve to increase access to CBT-I, as behavioral sleep medicine is currently underserved throughout much of the country.

Hypnotics

Medications are effective in the short-term treatment of insomnia, in non-pathologic sleeplessness, and in conditions where the environmental conditions are not conducive to desired sleep. For volitional sleep deprivation, drug therapy should not be a replacement for behavioral modification. In some situations to aid in altering behavior, short-term use of medication is an appropriate consideration. Below is Table 1 [33, 34], which discusses specific hypnotic medications.

In 2015, *suverexant* (*Belsomra®, Merck, Kenilworth, NJ, USA*) was introduced to the US market after being FDA-approved for insomnia. The drug has a novel mechanism of action; it is an orexin receptor antagonist. Additionally, *ramelteon* (*Rozerem® Takeda, Tokyo, Japan*) is a newer entry in the sleep medication armamentarium. The drug is a direct melatonin receptor agonist, which may make it particularly effective for circadian rhythm sleep disorders. It has the advantages of not being a scheduled drug and has approval for long-term use.

Special Use Sleep-Inducing Agents

Sodium oxybate (*Xyrem®, Jazz Pharmaceuticals, Dublin, Ireland*) shortens significantly the latency to sleep onset and rapidly induces deep sleep. Sodium oxybate is used to maintain sleep and decrease the occurrence of cataplexy in narcolepsy. Sleep is severely fragmented in narcolepsy, and the disrupted sleep contributes to the daytime impairments through sleep deprivation. Sodium oxybate is started at 4.5 grams divided into two doses: one at bedtime and one 4 hours later and titrated to effect or 6–9 grams/night. Sodium oxybate is a schedule III drug with moderate abuse potential. It is dispensed to the patient directly from the company after the patient and physician have been taught proper techniques for utilization.

Low-dose *doxepin* (*Sinequan®, Pfizer, New York, NY, USA; Silenor® Pernix, Morristown, NJ, USA*) (3 to 6 mg) is approved by the FDA for the treatment insomnia under the brand name Silenor. Doxepin inhibits the reuptake of serotonin and norepinephrine and is primarily used as an antidepressant. Doxepin is thought to exert its sedation effects through strong antagonism of H_1, H_2 receptors.

Trazodone hydrochloride (*Desyrel®, Locust Valley, NY, USA*) is a triazolopyridine derivative antidepressant unrelated to tricyclic, tetracyclic, or other known antidepressant agents. It is not FDA-approved for the treatment of insomnia but is widely used off-label nonetheless. Trazodone may be given at a starting dose of 50 mg nightly and raised to 100 mg nightly, if necessary. In depression, it is used at much higher doses of up to 400 mg per day divided into three doses. Male patients should be warned about the possibility of priapism, and female patients should be warned that trazodone is not recommended for use during pregnancy.

Quetiapine (*Seroquel®, AstraZeneca, Cambridge, UK*) is not recommended for use in insomnia. Quetiapine is an antipsychotic agent with antagonism of dopamine, serotonin, and histamine receptors, and somnolence is reported in up to 50% of patients. If the patient has insomnia associated with schizophrenia, bipolar disorder,

Table 1 Pharmacokinetic properties and dosages of some hypnotic drugs used in the treatment of insomnia

Hypnotic drugs[a]	Half-life (hr)	Onset of action (min)[b]	Pharmacologically active metabolites	Dose (mg)
Benzodiazepine hypnotics				
Quazepam ^{R_x} (Doral®, Galt Pharmaceuticals, Altanta, GA, USA)	48–120	30	*N*-desalkyl (flurazepam)	7.5–15
Flurazepam (Dalmane®, Valeant Pharmaceuticals, West Laval, Quebec, Canada)	48–120	15–45	*N*-desalkyl (flurazepam)	15–30
Triazolam ^{R_x} (Halcion®, Pfizer, New York, NY, USA)	2–6	2–30	None	0.125–0.25
Estazolam ^{R_x} (ProSom®, AbbVie, North Chicago, IL, USA))	8–24	Intermediate	None	1–2
Temazepam $^{R_{xc}}$ (Restoril®, Mallinckrodt, Staines, UK)	8–20	45–50	None	15–30
Loprazolam[d] (Dormonoct®, Hoechst Marion Roussel limited, Kansas City, MO, USA)	4.6–11.4	–	None	1–2
Flunitrazepam[d] (Rohypnol®, Hoffman-LaRoche, Basel, Switzerland)	10.7–20.3	Short	*N*-desmethyl (flunitrazepam)	0.5–1
Lormetazepam[d] (Loramet®, Wyeth-Ayerst labs, Collegeville, PA, USA)	7.9–11.4	–	None	1–2
Nitrazepam[d] (Alodorm®, AlphaPharm, Sydney, Australia)	25–35	Intermediate	None	5–10
Nonbenzodiazepine hypnotics				
Eszopiclone (Lunesta®, Sunovion pharmaceuticals, Marlborough, MA, USA)	6–9	Rapid	N-desmethyl zopiclone	2–3 adult 1–2 elderly
Zolpidem (Ambien®, Sanofi-Aventis, Paris, France)	1.5–2.4	Rapid	None	5–10 (age >65 year)
				10–20 (age <65 year)
Zaleplon ^{R_x} (Sonata®, King Pharmaceuticals, Britol, TN, USA)	1	Rapid	None	5–10

[a]Citations for kinetic information are found in Maczaj [62]

[b]Derived from Smith CM, Reynard AM: Essentials of Pharmacology. Philadelphia, WB Saunders, 1995, p 228, and other sources

[c]Originally formulated as a hard capsule in the United States, concerns with kinetics and efficacy led to reformulation of the preparation to a soft gelatin capsule with characteristics comparable with those of other marketed benzodiazepines of its class [63, 64]

[d]Not available in the United States

[e]Not yet on the market in the U.S. at the time of writing, the manufacturer has recently received an "approvable" letter from the FDA for 2 and 3 mg in adults and 1 mg in the elderly

[f]Drugs that do not have U.S. Food and Drug Administration (FDA) indications for aiding sleep. There is no FDA-recommended dose for this purpose. Doses are approximations of those often used in clinical practice

Modified with permission from Refs [33, 34]

or psychotic depression, then quetiapine may be considered for the primary FDA-approved indication.

For chronic insomnia, when patients are either unable or unwilling to pursue a course of CBT-I or do not respond to it, second-generation hypnotics such *as zolpidem and eszopiclone* are typically used on a chronic basis. Prior to embarking on this treatment plan, it is important to screen the patient carefully for other underlying primary sleep disorders, such as sleep apnea and PLMD and pursue polysomnography in those who are at high risk. Clinicians are cautioned to have regular follow-up with patients to ensure that hypnotic tolerance, dependence, or abuse is not occurring.

Pharmacological Treatments to Sustain Alertness in TBI

After disorders of initiating and maintaining sleep have been treated, if EDS remains, pharmacological treatments may be considered. The following is a list of some of the more commonly used medications and is not intended to be a comprehensive list:

- *Caffeine* ("*stay alert*," "*jolt*") 100 or 200 mg upon awakening and as needed. Effective for about 3–4 hours. Physiological manifestations, tolerance, withdrawal. Easy to obtain, large therapeutic window, essentially safe.
- *Modafinil* (*Provigil®, Teva Pharmaceutical, Petah Tikva, Israel*) 100 or 200 mg upon awakening. Novel drug with minimal physiological side effects. Effective for about 4–6 hours (schedule IV – low abuse potential).
- *Armodafinil* (*Nuvigil® Teva Pharmaceutical, Petah Tikva, Israel*) 150 or 250 mg upon awakening. R-enantiomer of modafinil. Effective for 8–10 hours (schedule IV – low abuse potential).
- *Dextroamphetamine* (*Dexedrine®, GlaxoSmithKline, Brentford, UK*) 10 or 20 mg upon awakening, physiological manifestations effective for 8–10 hours or longer (schedule II – high abuse potential), tolerance, withdrawal.
- *Methylphenidate* (*Ritalin®, Ritalin SR®, Novartis, Basel, Switzerland*) may be started at 5 mg twice daily**,** upon awakening and at noon, to increase attention and focus. Increases may be made in 5 mg/day increments until effective or until a dose of 20 mg twice daily has been achieved. Side effects outweigh benefits.

Emerging Pharmacological Treatment Options for Sleep Disturbance in mTBI

One double-blind, placebo-controlled study found that *N-acetylcysteine*, when given for 7 days following mTBI, resulted in decreased short-term sequelae, including sleep disturbance, compared with controls [35].

Specific Diagnostic Categories

In TBI patients, excessive sleepiness may be caused by exogenous factors, endogenous factors, or both and may be a symptom of sleep disorders, behavioral disorders, or physical disorders. *Exogenous factors* are those that arise from outside the body, including volitional, yet unintended, reductions in sleep time. Volitional reduction of sleep is the most common cause of sleep deprivation and EDS. Exogenous factors may lead to sleep deprivation-related sleep disorders, such as the extrinsic insomnias (e.g., inadequate sleep hygiene, behavioral, drug-induced), extrinsic circadian rhythm disorders (e.g., jet lag, shift work), and environmental sleep disorder. *Endogenous factors* arise from within the body, such as those associated with medical disorders and pain syndromes. Endogenous sleep disorders that lead to EDS and sleep deprivation include the intrinsic insomnias, sleep-related breathing disorders, and intrinsic circadian rhythm disorders.

Excessive Daytime Sleepiness and Sleep Deprivation-Associated Sleep Disorders Associated with Exogenous Factors

ICSD-3 [24], published in 2014, consolidated insomnia to three disorders: chronic insomnia disorder, short-term insomnia disorder, and "other" insomnia disorder. By changing the nosology, the ICSD-3 did away with the following insomnia subtypes as distinct disorders. Nevertheless, there is value in discussing them as they remain essential components of a thorough insomnia history.

Behaviorally Induced Insufficient Sleep Syndrome

The primary complaint is excessive sleepiness, and the primary historical feature is shorter than required habitual sleep time. The patients usually attempt to make up sleep when possible, such as on weekends. If polysomnography or a MSLT is performed, the results show at least moderate sleepiness (latency of <8–10 minutes) and highly efficient sleep (> 90%). Ruling out other causes of sleepiness is essential. Increases in sleep time

are both diagnostic and therapeutic. This is the classic volitional sleep deprivation syndrome.

Lifestyle choices are often the direct cause of fatigue and sleeplessness, although with many lifestyle choices the sleep deprivation is an acknowledged and inevitable component. For example, having a family is a lifestyle choice, with co-sleeping, nursing, and the immediate postpartum period, all resulting in sleep deprivation.

Long Sleeper

A small percent of the population (1–2%) appear to naturally require more than 8 hours of sleep per night. Long sleepers are defined as those requiring 9.5 hours sleep or more per night for well-rested daily function. If those individuals are restricted to less than their optimum sleep time by lifestyle constraints, such as school, work, or family, they will manifest with EDS and other associated symptoms of sleep deprivation. Behaviorally induced insufficient sleep syndrome may be difficult to diagnose in these individuals as they may present with a history of apparently normal sleep quantity.

Environmental Sleep Disorder

The essential feature of the environmental sleep disorder is an adverse sleep environment. The adverse environment may be too warm, too cold, too cramped, too loud, too motion-filled, etc. The level of the noxious environmental stimulus is less important than the effect of the stimulus on the patient, that is, the same stimulus may disrupt one individual's sleep while barely impacting another individual's sleep. The essential features are complaints of insomnia and EDS. The insomnia may not be recognized by the patient as being caused by a noxious environmental stimulus. The EDS may occur in the presence of an apparently normal amount of time in bed. Identification and exorcism of the noxious environmental feature is both diagnostic and therapeutic.

Inadequate Sleep Hygiene Disorder

Insomnia associated with poor sleep habits, and in the absence of other extrinsic or intrinsic causes, coupled with excessive sleepiness leads one to consider inadequate sleep hygiene disorder. As there are so many reasons for poor sleep habits, ruling out other more readily quantifiable causes of insomnia and excessive daytime sleepiness is essential. Similar to behaviorally induced insufficient sleep syndrome, the habits resulting in poor sleep hygiene may be voluntary, albeit unintended. Unlike behaviorally induced insufficient sleep syndrome, the time allotted to sleep may be completely sufficient. When both poor sleep habits and regularly decreased time in bed occur simultaneously, inadequate sleep hygiene disorder may be diagnosed as a secondary disorder.

Insomnia Due to a Drug or Substance

The essential feature of this disorder is an insomnia that can be related to a drug, substance, or drug withdrawal. Medications and withdrawal cause restlessness, insomnia, and tiredness. An incomplete list of medications includes hypnotics, antihistamines, major tranquilizers, beta-blockers, over-the-counter medications containing alcohol, and medication withdrawal such as caffeine withdrawal. EDS occurs episodically when sleep is sufficiently disrupted or reduced and may be associated with the daytime use of a stimulant drug such as caffeine. For example, if a patient excessively drinks coffee all week, then stops or reduces intake on a weekend, sleepiness may manifest on weekends, even if the patient has increased the amount of weekend time in bed. Insomnia due to a drug or substance may be a diagnosed as a contributing diagnosis in inadequate sleep hygiene disorder.

Circadian Rhythm Sleep Disorders

Excessive sleepiness, insomnia, and functional impairment are essential components of circadian rhythm sleep disorders. Two of the circadian rhythm sleep disorders are directly caused by exogenous factors: jet lag disorder and shift work disorder. Jet lag disorder is self-limiting and resolves with adjustment to the new time zone. Periods of adjustment vary from days to weeks depending upon the number of time zones crossed. Shift work disorder is not necessarily self-limiting and is often the cause of chronic

sleep deprivation. Some workers rotate among several shifts with inadequate time to compensate. Patients may experience pressure to remain awake during their scheduled sleep periods while performing shifts desynchronized from the majority of their family and friends.

Other Sleep Disorders that May Be Associated with Traumatic Brain Injury

Insomnia Due to a Medical Condition

The essential feature of this disorder is that insomnia is clearly linked to an identifiable medical condition. Indolent health problems cause sleepiness by interfering with both quality and quantity of sleep. Pain, such as may be caused by headache syndromes, neuropathies, musculoskeletal disorders, trauma, or surgical interventions, can cause insomnia and result in sleep deprivation. Physical health problems, such as asthma, may make sleeping difficult, while mental health problems, including depression and post-traumatic stress disorder, can also lead to insomnia. Excessive sleepiness varies according to both the degree of sleep deprivation and the functional level of the medically impaired patient. Treatment of the medical condition and resolution of the insomnia should resolve the EDS.

Circadian Rhythm Sleep/Wake Disorder Not Otherwise Specified (NOS) (Formerly Circadian Rhythm Disorder Due to a Medical Condition)

Excessive sleepiness results from sleep deprivation associated with the impaired circadian-rhythm-induced insomnia. Excessive sleepiness, insomnia, and functional impairment are essential components of all circadian rhythm sleep disorders, whether endogenous or exogenous.

Delayed Sleep/Wake Phase Disorder (Formerly Circadian Rhythm Disorder, Delayed Sleep Phase Type)

Individuals with early rising times due to school, work, or other regular obligations and with delayed sleep phase circadian rhythm disorder complain of excessive sleepiness and insomnia. Unable to sleep at the time, their families retire and unable to fall asleep early enough to obtain enough restorative sleep, these patients function below optimal efficiency. Delayed sleep phase patients may respond initially to hypnotics but will most likely return to their late sleep times upon discontinuation of the drug treatment or upon development of tolerance.

Sleep-Disordered Breathing Disorders

Excessive sleepiness may be a presenting complaint in the sleep-disordered breathing disorders. The excessive sleepiness is caused by the decreased quality and quantity of the fragmented sleep. Treatment of the underlying breathing disorder reduces the fragmented sleep and results in improved daytime alertness.

Sleep-Related Movement Disorders

Sleep-related movement disorders that significantly impair restorative sleep may result in excessive daytime sleepiness. Approximately 80% of patients with restless legs syndrome demonstrate excessive periodic limb movements of sleep (PLMS) on polysomnography. Additionally, PLMD is a separate sleep-related movement disorder where patients have excessive PLMS but no clinical restless legs syndrome (RLS) symptoms. PLMS often interrupt restorative sleep to the degree that complaints of daytime inattentiveness, easy fatigability, and excessive sleepiness interfere with daily functions. Dopamine agonists have traditionally been first-line treatment for both RLS and PLMD. However, the sleep medicine community has become increasingly aware that chronic use of these medications often leads to a phenomenon referred to as "augmentation." In this situation, the medication progressively loses its efficacy, followed by an inflection point where symptoms actually worsen. Due to concern about augmentation, α2δ drugs, such as gabapentin and pregabalin, are increasingly being used for initial treatment. Iron deficiency, defined as ferritin <50–75 ng/mL, has been determined to play a major role in RLS and PLMD, and it is suggested that iron studies be checked during workup for these disorders.

It is worth noting the emerging scientific body of evidence that suggests a relationship between mTBI and post-traumatic stress disorder (PTSD) [36, 37]. When occurring comorbidly, the etiology of the sleep symptoms may be unclear, as PTSD is associated with several sleep disorders, including sleep onset and maintenance insomnia and pseudo-REM sleep behavior disorder ("pseudo-RBD"), which is characterized by the tendency to act out dreams where the dream content is a reexperiencing of prior trauma. Unlike classical RBD, pseudo-RBD is not associated with neurodegenerative conditions.

Chronic traumatic encephalopathy, also known as dementia pugilistica, is characterized by motor, behavioral, and cognitive symptoms. Tremor, incoordination, Parkinsonian features usually appear early in the course of disease development. Behavioral changes include sleep disruption, most frequently insomnia. Volatility, agitation, and depression may develop. Usually progressive, the pathology develops from an accumulation of multiple head injuries, with many, if not most, being subclinical. The neuropathology is similar to Alzheimer's disease (AD), with neurofibrillary tangles and tau protein accumulations, but without the neuritic plaques typically seen in AD.

Individual Consequences of TBI, EDS, and Sleep Deprivation

Sleep deprivation results in a broad spectrum of physiologic changes. Decreases in brain glucose metabolism [38, 39], decreases in core body temperature [40], alterations in immune system function [41–43], fluctuations in hormone levels [44–48], and increased heart rate variability [49] have all been documented.

As the function of sleep has not been fully determined, the absolute number of hours necessary to fulfill its function remains unknown. Some individuals report full effectiveness with only 3–5 hours of sleep per night (short sleepers), while some admit needing more than 8 hours to perform effectively (long sleepers). Quantifying the effects of sleep deprivation may best be performed by reviewing the experimental literature.

Cognitive Performance

Among the most serious consequences of TBI-related sleep deprivation are insidious decrements in cognitive performance, which often are unrecognized by the affected individual. Both simple cognitive functions and more complex functions, such as situational awareness, judgment, and decision-making, are affected.

Speed Before Accuracy

With decreased sleep, higher-order cognitive tasks are affected early and disproportionately. Tests requiring both speed and accuracy demonstrate considerably slowed performance times before accuracy begins to fail [15, 50–53]. In chronic partial sleep deprivation studies, total sleep duration of 7 hours per night over 1 week resulted in decreased speed in tasks of both simple reaction time and in more demanding computer-generated mathematical problem-solving. Total sleep duration of 5 hours per night over 1 week results in both a decrease in speed and the beginning of accuracy failure [54].

Driving Performance

The National Transportation Safety Board (NTSB) [55] reports driver fatigue as a contributing cause of multiple automobile and truck accidents (SB03–15, SB04,-10, SB05–13). When total sleep time is reduced to 5 hours per night over 1 week, increased lane deviations and increased speed variability are seen, while when total sleep time is reduced to 3 hours per night, significantly increased accident rates occurred in driving simulator experiments [50, 54].

Visual Performance

Acute sleep loss beginning at 19 hours awake was associated with a decreased ability to simultaneously appreciate peripheral and central visual stimuli, suggesting a transient, sleep deprivation-

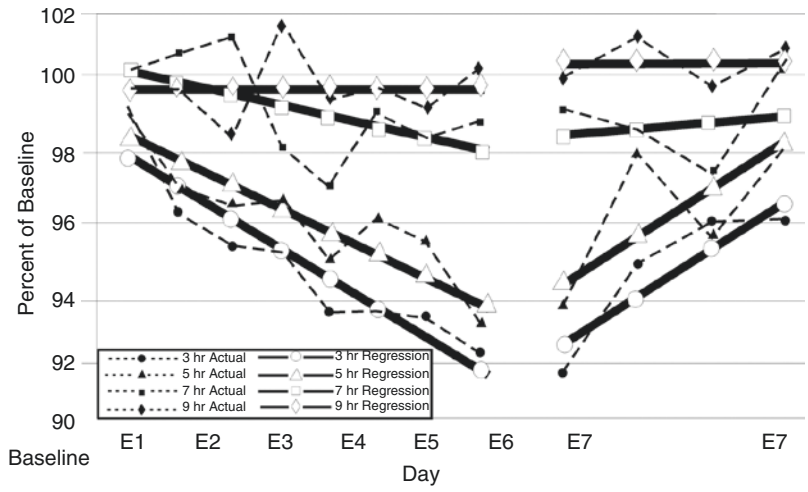

Fig. 7 Changes in group mean saccadic velocity with four doses of sleep (3, 5, 7, 9 hours) over a 7-night experimental period and 3-night recovery period. (Used with permission of Elsevier from Russo et al. [59])

induced visual simultanagnosia and peripheral neglect [56–58]. Oculometric measures have been shown to be sensitive to the effects of sleep deprivation. During multiple consecutive days of partial sleep deprivation, group mean saccadic velocity showed consistent daily decreases (Fig. 7) ordered according to the number of hours of sleep restriction [59]. Groups that received 3 and 5 hours of time in bed for 7 nights demonstrated highly significant negative slopes, about 0.75 and 0.50 mm/sec per day, respectively. Latency to pupil constriction shows similarly ordered effects across groups, with a significant positive slope in the 3-hour group.

In restricted sleep of 3 hours per night over 1 week, decreases in saccadic velocity correlated highly with increases in simulator driving accidents. Additionally, latency to pupil constriction increases were correlated with driving accident increases in the 3-hour group. Rowland and coauthors [60] found similarly high correlations between saccadic velocity, simulator driving accidents, latency to pupil constriction, and accidents in a study of continuous total sleep deprivation.

Of interest in the Rowland and coauthors [60] study was the result that only 1 night of recovery sleep after 2 nights of total sleep deprivation returned saccadic velocity and constriction latency to baseline, while in the chronic partial sleep deprivation study, 3 days of recovery sleep did not yield return to baseline of the same measures. Those findings suggest that the brain, vis-a-vis oculomotor function, may have been reacting to chronic partial sleep deprivation with an adaptation response mechanism that required substantially more time to recover from than an accommodation response from brief total sleep deprivation.

Judgment and Risk Taking

In tasks requiring judgment, increasingly risky behaviors emerge with total sleep deprivation. The high cost of an action seemingly is ignored as the sleep-deprived individual focuses on limited benefit.

Brain Metabolism Changes

Glucose-PET studies in individuals deprived of sleep have shown that after 24 hours of sustained wakefulness, the metabolic activity of the brain decreases significantly – up to 8% for the whole brain and up to 15% for specific cortical and basal ganglionic areas [38, 39]. These experimental findings can be explained by glucose-PET studies, which show that individuals deprived of sleep for 24 hours have a decrease in metabolism in the prefrontal, parietal association, and thalamic areas. The areas most important for judgment, impulse control, attention,

and visual association are disproportionately hypometabolic compared to the primary sensory and motor areas necessary for receiving and acting upon environmental inputs. This finding suggests that the areas of the brain most responsible for higher-order cognition are to some degree less functional during sleep-deprived waking activity. Areas involved with alertness are also metabolically deactivated with 24 hours of sustained wakefulness. Hypometabolism in these areas, along with the prefrontal and parietal associational areas, persists and, in some cases, increases across 48 and 72 hours of sustained wakefulness [39, 61].

Conclusions

mTBI is associated with a high incidence of sleep disorders of diverse types. Identification and management of sleep disorders in the mTBI population is important for improving quality of life and preventing further morbidities.

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Vestibular Consequences of Mild Traumatic Brain Injury (mTBI)

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Introduction

The vestibular organs are crucial for motion sensation and maintenance of balance. Imbedded in the temporal bones, they are well protected and yet vulnerable to concussive shock with abrupt force applied to the head through blunt trauma or overpressure from blasts. A variety of injuries can occur to the vestibular organ with traumatic brain injury (TBI), both acute and chronic. Dysfunction of the vestibular organs results in continuous or intermittent vertigo and reduction of balance, increasing the risk of falls. In addition, injury can occur in a number of places in the central vestibular pathway, which can also cause impairment in balance function and equilibrium.

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It is our opinion that vestibular dysfunction is often unrecognized after TBI, due to the attention paid to primary injuries to the scalp, skull, and brain. Rapid recognition of the possibility of vestibular disorders after TBI should lead to screening for these problems and their prompt treatment. The great advantage of such screening and recognition is that appropriate treatment can often be immediately rendered. For example, lack of identification of the presence of benign positional vertigo (BPV) can mean that as a head injury patient tries to mobilize they are struck with debilitating vertigo. This vertigo can result in falls and drastic exacerbation of patients' other symptoms, such as headache and memory loss. The patient is thus bedridden or mobility impaired for a long periods, even months. Fortunately, a simple treatment, the canalith repositioning maneuver [1], can immediately cure BPV and hugely improve mobilization and even mental status. Other vestibular disorders can also be detected and managed expeditiously to improve recovery. For example, a study of blast-injured service members in Operation Iraqi Freedom demonstrated improvement if their blast-triggered migraine-related vertigo was diagnosed and treated [2].

For the purposes of this chapter, we will confine our discussion to mild traumatic brain injury (mTBI), otherwise known as concussion. mTBI is the most common disorder seen in the wars in Southwest Asia and is increasingly becoming a more important topic due to the number of sports-related episodes of mTBI [2, 3]. The symptoms

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of this disorder can be myriad, but one of the most common is dizziness. Assessment for vestibular disorders should be part of standard clinical doctrine for acute and chronic management of head-injured patients. In this chapter, we will review this assessment from an anatomic and physiologic point of view and for the appropriate clinical approaches. We will briefly outline treatment approaches to the various disorders.

Vestibular Anatomy and Physiology

The vestibular organs are simply accelerometers that provide information to the brain about the motion of the head. Inside the utricle and the macula are the otolith organs. The otoliths are calcium carbonate crystals fixed in a gelatinous matrix that rest on hair cells. The otoliths are detectors of linear acceleration, either motion in a straight line or slow tilting of the head relative to horizontal. In contrast, the semicircular canals (SCC) are rotational or angular accelerometers. They are hollow and fluid-filled. Inertia of fluid in the canals as the head turns results in the deviation of the cupula, the acceleration sensor in each canal. Signals from the hair cells in the otoliths and the SCCs are transmitted along the vestibulocochlear nerve, in parallel with the signals from the cochlea that encode sound stimuli. In the brainstem, vestibular signals are combined, modulated, and adapted by cerebellar circuits. Disruption of the otoliths, SCCs, vestibulocochlear nerves, and brainstem circuits are all potential sites of dysfunction of the vestibular system. Active disturbance of these systems results in vertigo, and damage to the systems mean loss of acceleration information to the brain and loss of balance. Understanding of the pathophysiology, loss of function, and neural adaptation of the vestibular system is key to the management of TBI-induced disorders.

Mild Traumatic Brain Injury (mTBI) from Blunt Versus Blast Trauma

In this discussion we will examine two types of mTBI. We will first look at mTBI secondary to blunt head injury (closed head injury); then we will examine the vestibular disorders associated with mTBI seen after blast.

Blunt head injury is by far the most common cause of mTBI in the civilian world and is receiving increased attention due to sports-related etiologies. Such sports-related injuries can occur in high-profile professional athletes as well as the young soccer prodigy playing at the local park on Saturday morning. Work in our laboratory over the last several years has allowed us to characterize the neurosensory symptoms as a whole and individual vestibular disorders that were seen after closed head injury [4–6].

There are five well-described symptom clusters that individuals who have suffered mTBI will likely fall within [6]. These include (1) dizziness/mild cognitive impairment, (2) post-traumatic headache/migraine, (3) emotional/affective, (4) fatigue/malaise, and (5) nausea. The mTBI patients that fall within the dizziness/mild cognitive impairment cluster describe symptoms of balance problems, dizziness, difficulty concentrating, difficulty remembering, confusion, and blurred vision. There are also well-known differences between each sex, with more males exhibiting dizziness/mild cognitive impairment symptoms and more females exhibiting post-traumatic headache/migraine symptoms. Other factors likely play a role, such as the higher prevalence of headaches in women, but all of these symptom clusters are important to consider when assessing a recently injured patient in the emergency room or clinic setting.

Table 1 shows the characteristics of the four classes of balance disorders seen after blunt trauma. Post-traumatic benign positional vertigo (PTBPV) is identical to idiopathic benign positional vertigo. It is characterized by short episodes of vertigo that occur when changing head or body position (rolling over in bed, looking up, etc.). The episodes last only a few seconds. PTBPV is discussed in more detail below. Post-traumatic exercise-induced dizziness (PTEID) is dizziness that occurs after the completion of physical activity. These individuals complain of unsteadiness or feeling off balance after they finish a period of physical exertion. They do not generally complain of vertigo. The third class of dizziness seen is post-traumatic

Table 1 Vestibular disorders after closed head injury

Entity	History	Physical exam	Vestibular tests
Positional Vertigo (PTBPV)	Positional Vertigo	Nystagmus on Dix-Hallpike test or modified Dix-Hallpike test	No other abnormalities
Exertional Dizziness (PTEID)	Dizziness during and right after exercise	Abnormalities in challenged gait testing	No other abnormalities
Migraine-associated dizziness (PTMAD)	Episodic vertigo with periods of unsteadiness Headaches	Abnormalities in challenged gait testing +/− Abnormalities on head impulse testing. Normal static posture tests	VOR gain, phase, or symmetry abnormalities. High-frequency VOR abnormalities Normal posturography
Spatial disorientation (PTSpD)	Constant feeling of unsteadiness worsened by standing but still present when sitting or lying down Drifting to one side while walking. Shifting weight when standing still	Abnormalities on standard gait tests +/− Abnormalities on head impulse testing Abnormalities on static posture tests	VOR gain, phase, or symmetry abnormalities. High-frequency VOR abnormalities Abnormal posturography Central findings on rotation chair testing

migraine-associated dizziness (PTMAD). In this classification, which has received increasing attention over the last several years, individuals complain of a variety of transient types of dizziness. Individuals can have vertigo, unsteadiness, or visual flow abnormalities. The episodes are intermittent and can last from seconds to hours. Most have more than one type of dizziness episode. In this disorder, migraine headache (either coincident with or distinct from the dizziness) is one of the hallmark symptoms. PTMAD is discussed in more detail below. The final class of dizziness seen after blunt head trauma is post-traumatic spatial disorientation (PTSpD). In this symptom complex, individuals complain of unsteadiness when standing still or moving quickly. They also have unsteadiness on uneven surfaces or when walking in poor light conditions. Similar to the migraine-associated dizziness patients, this group of individuals may have headaches, but unlike that group, headaches are rarely one of the dominant symptoms. The hallmark of this condition is the need to use light touch when standing still to avoid wobbling. We have been able to describe the frequency of these disorders, and these data are shown in Fig. 1. It should be noted that the frequency of PTBPV is likely underestimated in this group since many of these individuals may have resolved the BPV prior to presenting to clinic.

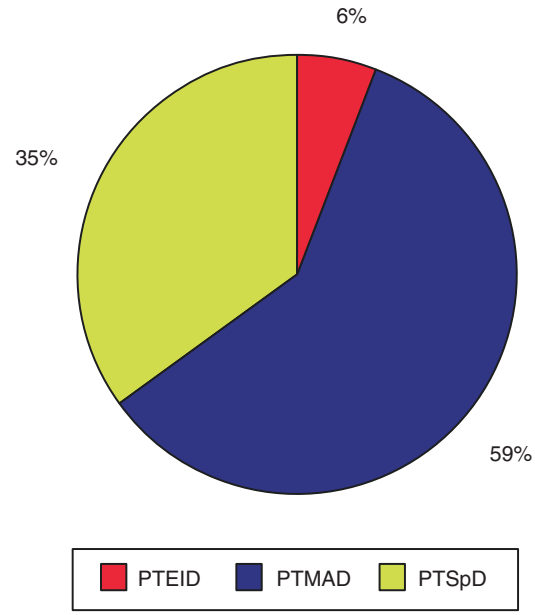

Fig. 1 Comparisons of dizziness. Blunt head trauma

While blast-related mTBI may seem less relevant, it is becoming an increasingly important etiology of mTBI. Well over 80% of all war injuries are blast-related mTBI in isolation. In the civilian world, air bags, compressors, pneumatic tools, and a number of other job site risks have resulted in a sharp rise in the number of blast-related mTBI cases. Dizziness is the leading symptom of blast-related mTBI [2]. Blast-induced mTBI differs from blunt mTBI in a number of ways [5]. The

Table 2 Balance disorders seen after blast exposure

Entity	History	Physical exam	Vestibular tests
Positional Vertigo (PBBPV)	Positional vertigo	Nystagmus on Dix-Hallpike test or modified Dix-Hallpike test	No other abnormalities
Exertional dizziness (PBED)	Dizziness during exercise	Abnormalities in challenged gait test	No other abnormalities
Blast-induced disequilibrium (PBD)	Constant feeling of unsteadiness when standing and walking worse with challenging environments Constant headache	Abnormalities in challenged gait Abnormalities in tandem Romberg Abnormalities with quick head motion	Abnormal posturography Abnormal target acquisition, dynamic visual acuity, and gaze stabilization +/-VOR gain, phase, or symmetry abnormalities
Blast-induced disequilibrium with Vertigo (PBDV)	Constant feeling of unsteadiness when standing and walking worse with challenging environments Constant headache Episodic vertigo	Abnormalities in challenged gait Abnormalities in tandem Romberg Abnormalities with quick head motion	Abnormal posturography Abnormal target acquisition, dynamic visual acuity, and gaze stabilization VOR gain, phase, or symmetry abnormalities

classes of dizziness demonstrate the differences between blast and blunt TBIs effects. Table 2 shows the classes of dizziness seen after blast-induced mTBI. The post-blast benign positional vertigo (PBBPV) is identical to that of PTBPV with transient positional-induced vertigo episodes. On the other hand, post-blast exertional dizziness (PBED), which was formerly termed post-blast exercise-induced dizziness, is dramatically different from the PTEID in that post-blast individuals get unsteady upon starting to exercise (rather than at the completion of the episode). The symptoms of unsteadiness and disequilibrium as well as headaches are the same but the temporal relationship of these symptoms to the exercise is much different and, hence, more troubling to the patient. The final two classes, post-blast dizziness (PBD) and post-blast dizziness with vertigo (PBDV), are characterized by the following two symptoms – constant unsteadiness, which is made worse by more challenging balance environments (uneven surfaces, poor light conditions, moving quickly, etc.) and constant headaches which fluctuate in severity. The presence of additional episodic vertigo separates the two disorders. The relative frequency of these dizziness types is shown in Fig. 2. Unlike after blunt head injury, the frequency of PBBPV, while likely slightly higher than zero, is very small. The classification systems have proved

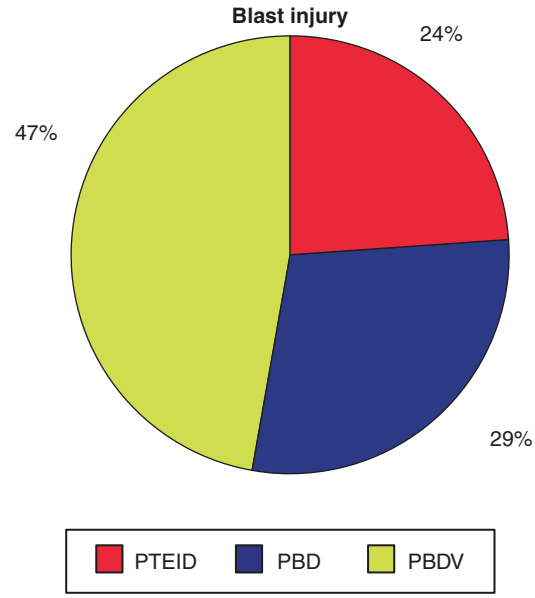

Fig. 2 Comparisons of dizziness. Blast injury

helpful in a variety of ways. They can be understood and are essential to guide treatment and rehabilitation. They also provide prognostic details that help in patient management. Equally as important is that they provide a diagnosis for patients who have too often been told that the dizziness is "something they got from the head injury" and "give it time – it will go away."

Post-traumatic Benign Positional Vertigo (PTBPV)

BPV is the most common condition causing vertigo. BPV is simply the result of calcium carbonate crystals broken loose from the otolith organ ending up in the semicircular canals. Clinicians involved in the diagnosis or treatment of patients that present with vertigo or imbalance should know how to elicit a history of BPV and carry out the Dix-Hallpike test for the diagnosis. The canalith repositioning maneuver (CRM or, as it is commonly known, the Epley maneuver) is a simple, safe procedure that can immediately cure BPV. If one is familiar with the diagnosis of BPV, the CRM is a powerful addition to one's armamentarium. A full description of the Dix-Hallpike test and the CRM is given in Viirre and colleagues [7]. In summary, one looks for a history of brief vertigo attacks that are provoked by head movements: rolling over in bed, bending over, or reaching up. The vertigo lasts seconds and should stop as soon as the patient lies still. Note that motion sickness and imbalance from a spell of BPV can last for minutes or hours after the actual vertigo episode. The Dix-Hallpike test is carried out with a patient on an examining bench. While being held securely by the examiner, the patient's head is turned 45 degrees to the right or left. The patient is then thrust backward rapidly. Onset of a vertigo sensation accompanied by torsional nystagmus (a clockwise or anticlockwise rotation of the eyes as the patient looks straight ahead) is diagnostic. The CRM is a simple continuation of movements once a positive Dix-Hallpike test is elicited. With the head extended back so it is below the horizontal plane, a sequence of turns of the head and body will remove the offending calcium carbonate crystals from the semicircular canal.

Post-traumatic Migraine-Associated Dizziness (PTMAD)

Migraine is one of the most common genetic disorders present in approximately one in six women and one in ten men. Migraine is a disease complex of which headache is only the most common symptom. Migraine aura is well recognized and its presence is diagnostic of migraine. Almost half of migraineurs have dizziness and vertigo episodes [8]. The high incidence of migraine in the general population suggests that a high percentage of people with TBI will have concomitant migraine, even if they were not symptomatic prior to their injury. The physical and emotional stress of TBI – and perhaps the release of neurohumoral factors during the injury – are powerful triggers for migraine symptoms. The post-traumatic headache, dizziness, cognitive difficulties, and symptoms not localized to the head may well be present in TBI patients as the result of activation of migraine.

Migraine headache is diagnosed by using the International Headache Society criteria for headache [9]. There are no diagnostic criteria for migraine-related dizziness, but vertigo in a patient who meets the migraine headache criteria must have migraine considered in the differential diagnosis. Because of the variable penetrance of the condition, review for a family history of recurrent headaches, dizziness, and/or motion sensitivity may be fruitful, even if a formal diagnosis of migraine is not reported in the family.

Treatment of migraine can be effectively carried out by lifestyle and medical management. In TBI patients, particular attention must be paid to provision of adequate regular sleep, regular meals, and a well-designed activity program (see below). Medical management includes use of beta-blockers (propranolol) and carbonic anhydrase inhibitors (topiramate). Topiramate in particular has been studied in the TBI dizziness population and has been found to be effective not only for the dizziness and vertigo, but also for headache control in patients.

Diagnosis

Aside from a thorough medical history and a standard vestibular physical exam, there are recently described techniques to more accurately diagnose mTBI. These specialized vestibular function tests are identical to the standard clinical

vestibular exam but instead objectively measured with infrared goggles and standardized visual stimuli [10]. These tests can be separated into oculomotor tasks (vertical and horizontal smooth pursuit, vertical and horizontal saccades, antisaccade, predictive saccade, optokinetic response, saccade-reaction time test), vestibular tasks (head impulse test [HIT], subjective visual vertical and horizontal), and oculovestibular reaction time (OVRT) tasks.

A test battery consisting of a subset of these tests (antisaccade [increased error rate percentage], predictive saccade [decreased absolute number], and HIT tasks [increased absolute gain symmetry, decreased average gain]) can sensitively and specifically (89% and 95%, respectively) identify individuals with acute mTBI [10]. These tasks reflect underlying pathophysiologic differences in individuals who have suffered acute mTBI compared to healthy individuals. The increased antisaccade error rate suggests impaired inhibitory contributions of frontal cortical regions and GABAergic output from various brain regions [11]. The abnormal HIT results are presumed to be a result of disruption to neuroanatomical pathways involving the vestibular nuclei, related cerebellar connections, and direct projections from the oculomotor, trochlear, and oculomotor nuclei. Other sets of these tests yield similar specificity and sensitivity measurements and have been formatted to work on a pair of portable goggles. This portable system provides objective, point-of-injury testing and should also yield the best prognostic information for return to play as well. This body of recent work has begun to show that objective vestibular testing is considered to be an efficient and effective method to determine the presence or absence of mTBI.

Treatment

The vestibular physical therapy rehabilitation strategy employs specific exercises designed to decrease dizziness, increase balance function, and increase general activity levels. Exercises to decrease dizziness focus on exposure to specific stimuli for habituation or attenuation of the dizziness response in the brain. Balance retraining involves exercises designed to improve organization of sensory information for balance control and coordination of muscle responses. General activity exercise involves a daily aerobic exercise program of progressive walking, cycling, or swimming.

A vestibular physical therapy (VPT) program for mTBI patients consists of exercise procedures that target the vestibulo-ocular reflex (VOR), cervico-ocular reflex (COR), depth perception (DP), somatosensory retraining (SS), dynamic gait, and aerobic function. The VOR, COR, and DP exercises are graded in difficulty, based on velocity of head and object motion and progression of body positioning from sitting to standing to walking. The SS exercises are graded in difficulty by narrowing the base of support, making the surface uneven, or changing the surface from firm to soft. Large amplitude head and trunk movements are also employed to increase somatosensory input. These exercises include the proprioceptive neuromuscular facilitation techniques of slow reversal head and neck patterns, modified chopping and lifting for head and trunk in progression from supine to sitting to standing postures, and total body mass rolling activities. Varied walking exercises are graded in difficulty by changing direction, performing with the eyes closed, increasing speed of ambulation, walking on soft surfaces, or navigating stairs. An aerobic exercise home program progressively increases the time, speed, or distance that the patient can tolerate. All persons are encouraged to work at their maximum tolerance while performing the VPT. Patients are instructed to perform the exercises twice daily at home. Patients are monitored by the physical therapist twice the first week and once a week for the subsequent 7 weeks. Patient compliance to the home exercise program is surveyed by the physical therapist during patient visits.

An objective assessment is performed for all mTBI patients by the vestibular physical therapist. A functional test battery consisting of an impulse head thrust test, Fukuda step test, Romberg test, tandem Romberg test, and Dynamic Gait Index (DGI) [12] is administered

to each patient. In addition, the Dizziness Handicapped Index (DHI) [13] and the Activities-Specific Balance Confidence Scale (ABC) [14] surveys are administered. The above measurements are obtained pre-treatment, during treatment, and post-treatment (6–8 weeks after beginning treatment). Subjective patient reports of degree and length of imbalance perception are documented throughout treatment. The length of time required for patients to return to work after the initiation of physical therapy is monitored.

Patients are instructed to perform the exercises twice daily at home. Patients are monitored by the physical therapist twice the first week and once a week for the subsequent seven weeks. Patient compliance to the home exercise program is surveyed by the physical therapist during patient visits.

As we have noted, vestibular complaints are the most frequent sequelae of blast-induced mTBI [1]. VPT has been established as the most important treatment modality for this group of patients. Nevertheless there is little work objectively documenting the impact of VPT on this group of patients. Studies have been completed in the past examining clinical measures, like the Glasgow Coma Score (GCS), on overall recovery pattern after TBI, but outcome measures specifically aimed at examining the adequacy of vestibular tests to track vestibular recovery have remained lacking. Scherer and Schubert reinforced the need for best practice vestibular assessment for formulation of appropriate VPT treatment strategies [15]. Now the application of vestibular testing and rehabilitation in this patient population is needed to provide information on objective outcome measures [15]. VPT is most effective when applied in a customized fashion. While we and others have developed VPT procedures that are applied in "best practices" for blast mTBI vestibular patients, these therapies must be customized for the patient entry level of function and expectation level of recovery. Knowledge of the patient's disability and diagnosis is critical to build the foundation for return to activity, work, or sport. There has been documentation on the reliability of both the Center of Dynamic Pressure and the Dynamic Gait Index as diagnostic tools [12, 16–18], but those studies have not looked at the head injury population, which tends to have a different type of vestibular profile than those tested in previous studies. The head injury population is also a younger population than the previous studies represent. Similarly, there are several studies [19–22] examining the GCS as an outcome measure and correlating this with postural stability. In these studies the patient groups were small and again far different from our mTBI blast patients, both in terms of vestibular dysfunction and age. What might be considered normal for an older vestibular patient (post-stroke, etc.) would still be wholly unacceptable in this young military population intent on returning to active duty. Our study represents a demonstration of a suite of vestibular tests successfully utilized to judge outcomes in patients with both blunt and blast-induced mTBI with vestibular disorders. Vestibular clinical centers will establish their own normal levels on patients of similar age and activity level. The standard results of these tests can be used to determine return to duty/work status as well as return to physical activity status. While the entire suite of tests provides valuable information, our data indicate that the vertical GST is the most sensitive outcome predictor for our population. This likely indicates that recovery of vestibular function is frequency and velocity dependent. This observation agrees with the work of Paige [23] in which linearity and symmetry of the VOR were examined.

Advanced Concepts in Vestibular Consequences of TBI

Blunt and blast mTBI have been demonstrated to result in a variety of medical conditions and syndromes. These vary from simple diagnosis and management, such as BPV, to the more complex, such as post-traumatic spatial disorientation. Fortunately, observers can be readily trained to recognize these various conditions and initiate management. Since dizziness is the leading complaint post-mTBI, deployment of formalized protocols and training programs should be activated throughout the military and even in civilian envi-

ronments, such as organized football, where mTBI is frequent. Variants, such as migraine-related mTBI syndromes should be trained on for recognition and screened for management.

Despite recent work in the area, there is still a great deal of research with respect to mTBI that needs to proceed. Critical among these include deploying known countermeasures for mTBI, determining the pathophysiology of mTBI so even more specific treatments can be developed, studying the effects of multiple blasts and head impacts, and developing diagnostic and therapeutic tools that are mobile, rugged, and easy to use.

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Post-traumatic Headache

Ajal M. Dave, Jay C. Erickson, and Brett J. Theeler

Definitions

Headaches are classified as either primary or secondary headache disorders or a combination of both [1]. Primary headaches are not caused by an identifiable underlying illness, injury, or exposure. Examples include tension-type headache and migraine. In contrast, secondary headache disorders occur in close temporal relationship to another disorder that is known to cause headache [1]. Even if a secondary headache disorder shares the characteristics of a primary headache disorder, it is not classified as such. The exception to this is when a preexisting primary headache disorder becomes significantly worse in close temporal relationship to a causative disorder or event, in which case both the primary and secondary headache diagnoses should be given [1]. Causes of secondary headache disorders include trauma or injury to the head and/or neck; cranial or cervical vascular disorder; nonvascular intracranial disorder; substance or its withdrawal; infection; disorder of homoeostasis; disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structure; or psychiatric disorder [1]. Post-traumatic headaches (PTHAs) are among the most common types of secondary headache disorders [1]. Traumatic brain injury (TBI) is classified as mild, moderate, or severe by the Department of Defense (DOD) [2]. The terms concussion and mild TBI (mTBI) may be used interchangeably, and we will use the term concussion exclusively.

According to the *International Classification of Headache Disorders*, third edition (beta version) (ICHD-3 beta), headaches attributed to trauma or injury to the head and/or neck include six different secondary headache syndromes: acute PTHA, persistent PTHA, acute and persistent headache attributed to whiplash, and acute and persistent headache attributed to craniotomy [1]. PTHAs begin within 7 days of injury or within 7 days of regaining consciousness following injury. PTHA is further categorized as acute or persistent with headache lasting greater than 3 months [1]. The diagnostic criteria for acute PTHA, persistent PTHA, and delayed-onset acute PTHA attributed to moderate or severe traumatic injury are summarized in Box 1. Both acute PTHA and persistent PTHA are divided based on whether the injury was mild or moderate/severe [1]. Moderate/severe injury is distinguished based on the presence of at least one of the following criteria listed under A5.1.1.1 (B) in Box 1. Mild injury is distinguished by the absence of A5.1.1.1 (B) criteria but the presence of at least one of the following immediately after injury: transient confusion, loss of consciousness <30 minutes, disorientation, loss of memory for the event, nausea, vomiting, visual disturbance, dizziness, vertigo,

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impaired memory, or impaired concentration [1]. Delayed-onset acute PTHA may also be due to mild injury [1]. There is also a classification for delayed-onset persistent PTHA due to mild or moderate/severe injury [1]. The term "persistent" should not be confused with the term "chronic," which signifies greater than 15 headache days per month when applied to headache disorders [1, 3–5]. The criteria for acute and chronic headache attributed to whiplash injury are similar but imply acceleration/deceleration movements of the head, with flexion/extension of the neck [1].

Box 1 Diagnostic criteria for acute and persistent headache attributed to traumatic injury to the head

5.1 *Acute headache attributed to traumatic injury to the head*

- A. Any headache fulfilling criteria C and D
- B. Traumatic injury to the head has occurred
- C. Headache is reported to have developed within 7 days after one of the following:
  1. The injury to the head
  2. Regaining of consciousness following the injury to the head
  3. Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head
- D. Either of the following:
  1. Headache has resolved within 3 months after the injury to the head.
  2. Headache has not yet resolved, but 3 months have not yet passed since the injury to the head.
- E. Not better accounted for by another ICHD-3 diagnosis

5.2 *Persistent headache attributed to traumatic injury to the head*

- A. Any headache fulfilling criteria C and D.
- B. Traumatic injury to the head has occurred.
- C. Headache is reported to have developed within 7 days after one of the following:
  1. The injury to the head
  2. Regaining of consciousness following the injury to the head
  3. Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head
- D. Headache persists for >3 months after the injury to the head.
- E. Not better accounted for by another ICHD-3 diagnosis.

A5.1.1.1 *Delayed-onset acute headache attributed to moderate or severe traumatic injury to the head*

- A. Any headache fulfilling criteria C and D
- B. Traumatic injury to the head has occurred, associated with at least one of the following:
  1. Loss of consciousness for >30 minutes
  2. Glasgow Coma Scale (GCS) <13
  3. Post-traumatic amnesia lasting >24 hours
  4. Alteration in level of awareness for >24 hours
  5. Imaging evidence of a traumatic head injury such as intracranial hemorrhage and/or brain contusion
- C. Time of onset of headache is uncertain and/or headache is reported to have developed >7 days after all of the following:
  1. The head injury
  2. Regaining of consciousness following the head injury (when applicable)
  3. Discontinuation of medication(s) that impair ability to sense or report headache following the head injury (when applicable)
- D. Either of the following:
  1. Headache has resolved within 3 months after the head injury.
  2. Headache has not yet resolved but 3 months have not yet passed since the head injury.
- E. Not better accounted for by another ICHD-3 diagnosis.

Modified with permission from Headache Classification Committee of the International Headache Society (IHS) [1]

The current requirement that headaches must begin within 7 days of injury or regaining consciousness is somewhat arbitrary [1, 4]. There are data to support that current time cutoffs are leading to an underestimation of the prevalence of PTHA [6]. Approximately 20–30% of PTHAs occur after 1 week, but within 1 month, in military and civilian studies, and time periods as long as 6 months have been suggested given the low probability of a migraine headache developing in a predominantly male, otherwise healthy patient population [7–9]. A shorter time interval allows for higher specificity [1, 4] with a loss in sensitiv-

ity [1]. To address this area of uncertainty, the ICHD-3 beta includes appendix criteria A5.1.1.1 *Delayed-onset acute headache attributed to moderate or severe traumatic injury to the head* and A5.1.2.1 *Delayed-onset acute headache attributed to mild traumatic injury to the head* to be used when the interval between headache and injury is greater than 7 days [1].

The current 3-month time criteria used to differentiate between acute and persistent PTHA has come under scrutiny as it is based upon observational studies rather than biologic mechanisms [10–12], with some suggesting a 6- or 12-month interval to distinguish between acute and persistent PTHA [4].

Epidemiology

Approximately 1.7 million people sustain a TBI in the United States annually [3, 6, 13, 14], with 76% being classified as concussion [3, 6, 14]. Headache is the most common symptom following TBI [3, 6, 7, 13–17], with a prevalence of 30–90% at 1 month post-injury [6, 7, 16, 18–20]. PTHAs tend to decline over time. In a longitudinal study of 452 patients that followed after a moderate and severe traumatic brain injury, the cumulative incidence of headache and frequent headache steadily increased over 12 months, but the incidence rate tended to plateau at about 3 months after the injury [9]. Only 18% of participants continued to have PTHAs at 3 months post-injury, and between 3 and 12 months, the incidence of new headache was approximately 20% [9]. The authors also surveyed participants for frequent headaches, which were defined as headaches that occurred several times a day or daily 3 months post-injury. Eighteen percent of participants were having frequent headaches, and the total cumulative incidence of frequent headaches over the first year was 31% [9]. The PTHA incidence rates reported in that study are summarized by the authors in Fig. 1.

The epidemiology of headache after a whiplash injury is less well defined as no formal reporting system exists [21]. Of the patients suffering whiplash, 50% [22] will continue to have symptoms 6 months following injury, with up to 30% reporting moderate to severe pain or disability. Headaches occur immediately after whiplash injury in as high as 82% [21] of patients and chronic symptoms lasting a year or longer were reported in 15–21% of patients [21]. According to the current classification system, headaches that develop beyond 7 days after whiplash injury are not classified as headache attributed to trauma or injury to the head and/or neck [1].

There is an inverse relationship between the severity of head injury and the incidence of PTHA. PTHA is more likely to occur following concussion compared to more severe TBI [3, 7,

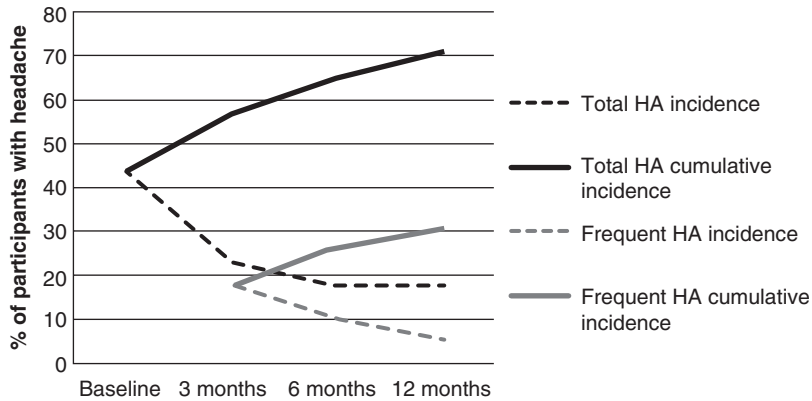

Fig. 1 Incidence and cumulative incidence of total headache in a group of 452 civilians in an acute inpatient rehabilitation program after a moderate or severe traumatic brain injury. The total headache incidence equals the fraction of subjects who first developed a headache at each time point. (Used with permission of Mary Ann Liebert Inc. from Hoffman et al. [9])

13, 19, 23, 24]. Prior history of headache was an independent risk factor for PTHA regardless of TBI severity [3, 6, 7, 13], whereas female gender [3, 6, 7, 13, 17] was a stronger risk factor when an individual sustained moderate or severe TBI rather than concussion [7]. Family history of migraine [3] and age (≤60) [13] were risk factors for the development of PTHA.

The incidence of acute PTHAs in children is 30–80%, a rate similar to that seen in adult populations [25, 26]. PTHAs tend to resolve in the majority of children within a year [25–27]. A prospective pediatric cohort study found that persistent PTHAs have a prevalence of only 7.8% among children after head injury [26, 27].

There is a disparity in the prevalence of PTHAs in different countries which may relate to social, ethnic, and cultural factors. Prospective studies in Lithuania and Australia, for example, revealed 3-month PTHA incidence rates of 11% [28] and 15% [29], respectively. The lower prevalence of PTHA in certain countries may be explained by different cultural and social expectations of post-traumatic symptoms [24] as well as lower rates of litigation [4, 21, 24, 30] in those countries. Headache was also the most common incident diagnosis made following TBI in US military service members serving between 2000 and 2012 [3].

In a study of Operation Enduring Freedom (OEF)/Operation Iraqi Freedom (OIF) US Army soldiers with concussion(s) during a combat deployment, 37% of soldiers met the time criterion for PTHA with another 20% of soldiers having headache onset outside of 1 week but within 1 month of a concussion [8]. PTHA in the military population occurs most often following blast exposure [6, 7, 23] and can be especially debilitating, meeting criteria for chronic daily headache (15 or more headache days per month) in up to 20% of cases [8]. Only 18% of military personnel evacuated to Germany during the OIF/OEF conflicts with PTHAs returned to duty; notably this was the lowest return to duty rate among all headache types [7].

The prevalence of post-traumatic stress disorder (PTSD) in US military service members deployed in support of OIF/OEF is between 5 and 20% in questionnaire-based studies [31, 32]. The number of US military service members deployed between 2002 and 2015 with a clinician-confirmed diagnosis of PTSD is 138,197 or between 3 and 6% of service members [33, 34] In civilian populations, PTSD is present in 29–75% of those suffering from PTHA [3, 31]. Patients with PTHA and comorbid PTSD are more likely to have headaches of greater severity [31] and are also more likely to endorse associated nausea and vomiting [31]. US Army soldiers that deployed and experienced combat were more likely to suffer from new-onset headache disorders post-deployment than soldiers that deployed but did not experience combat, emphasizing the potential link between PTSD, PTHA, and chronic headache disorders in military and civilian populations [7].

Pathophysiology

There are multiple pain-sensitive anatomic structures of the head and neck which are capable of causing head pain. The trigeminal nerve is the major pathway for transmitting nociceptive stimuli for the head (Fig. 2). The trigeminal nerve contains nociceptive afferents from the anterior scalp, anterior cranium, face, mouth, teeth, temporomandibular joints, sinuses, cranial blood vessels, and meninges. Injury to any of these structures can cause head pain. The greater and lesser occipital nerves, which arise from the C2 and C3 cervical spinal roots, convey nociceptive stimuli from the posterior head and scalp (Fig. 2). Painful stimuli from structures of the cervical spine are conveyed largely by the cervical nerve roots. The central processes of trigeminal pain neurons and cervical pain neurons converge within the central nervous system in the upper cervical spinal cord. The convergence of these two anatomic pain pathways is known as the trigeminocervical complex [35]. Some second-order neurons in this region receive inputs from both cervical and trigeminal pain afferents. Thus, peripheral activation of one pain system (trigeminal or cervical) can produce central activation of the other system. The trigeminocervical complex helps explain why injury of neck structures can

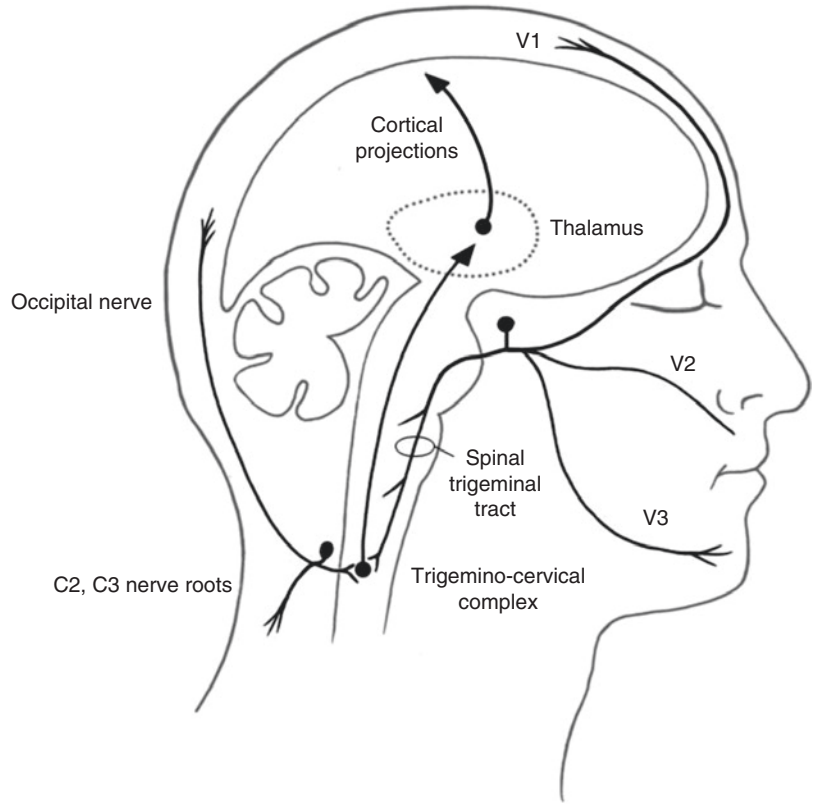

Fig. 2 Major neuroanatomic pathways conveying pain from the head and neck

cause head pain. It also helps explain why activation of the trigeminal pain pathway can produce pain in the posterior head and neck.

Headaches following concussion or mild head injury are rarely associated with an identifiable underlying structural injury [3, 18]. The definitive reason as to how head injury causes PTHA is not known, but one theory focuses on neurogenic inflammation [14]. Neurogenic inflammation may be caused by direct injury to the trigeminal afferents or the leptomeningeal or cerebrovascular structures innervated by the trigeminal nerves [14]. Neurogenic inflammation leads to locally increased blood flow [3, 14], as well as leakage of plasma proteins from blood vessels, mast cell degranulation [4, 14], and platelet aggregation [14]. The hallmark of neurogenic inflammation is a local inflammatory response from glial cells [3, 14]. Glial cells are CNS-resident immune cells that activate in response to pathogens or injury in the intraparenchymal space [3, 14]. Activated glial cells begin production of pro-inflammatory substances, including complement factor, cytokines [3, 14], chemokines [3, 14], proteolytic enzymes, and reactive oxygen and nitrogen species [14]. Pro-inflammatory substances are thought to be involved in the development and persistence of pain [3, 14].

Others theorize that TBI activates the transient receptor potential V1 channel, which enhances calcitonin gene-related peptide (CGRP) release from nociceptive trigeminal ganglia neurons [7]. CGRP is a potent vasodilator involved in neuroinflammation and pain modulation which can cause dilatation of meningeal arteries leading to PTHA with a migraine phenotype [7]. Patients suffering from chronic migraine will have interictal increases of CGRP [2]. Serotonin may be protective against the initiation of headaches as activation of serotoninergic (5-HT) receptors inhibits the release of CGRP, constricts painfully dilated cerebral blood vessels, and inhibits nociceptive neurotransmission in trigeminal pathways [36]. TBI can cause diffuse axonal injury

(DAI) which can damage long serotonergic axons leading to an initial increase in serotonin following injury followed by a decline several days after injury that can persist [36]. A persistent decline in serotonin levels following injury may lead to the development of headaches with a predominantly migraine phenotype [36]. CGRP may be co-regulated with pituitary adenylate cyclase-activating peptide (PACAP), which is a known migraine trigger that regulates cellular stress response and causes vasodilation of meningeal and trigeminal ganglia arteries [7].

Patients suffering from chronic PTHA (CPTHA) were compared with controls and found to have decreased thermal sensation (thermal hypoesthesia) and decreased pain response (hypoalgesia) in both painful regions of the head and painless regions of the hand [3, 12], indicating impaired spinothalamic and trigeminothalamic tracts in patients suffering from CPTHA [3, 12]. When patients suffering from CPTHA were compared with controls for joint position sense, no difference was found, indicating preservation of the dorsal columns [12]. Impairment of the spinothalamic and trigeminothalamic tracts with preservation of the dorsal columns is consistent with a central pain process [3, 12].

During trauma, occipital nerves, trigeminal nerves, or other peripheral nerves [4] may become irritated, activated, or compressed causing headache. This can result in neuralgic pain in the distribution of the nerve. Other structures that could become damaged by trauma or injury include vertebrae [4], face joints [4], or musculature, which can cause pain to be referred to the head.

The multiple mechanisms of head pain described above are not exclusive of one another. A patient may have multiple mechanisms acting in concert. Therefore, identifying all potential sources of head pain in each patient is important for developing a successful therapeutic plan.

Clinical Features

PTHAs are highly heterogeneous, both clinically and mechanistically, and many different headache types have been reported after head trauma [23]. PTHAs do not possess any unique clinical symptoms that clearly distinguish them from nontraumatic headache disorders, other than having the onset in close temporal relationship to head or neck trauma [1, 23]. In civilian populations, the most common painful region was the temple (82% of individuals) followed closely by the forehead (76.5%) and neck (76%). A large proportion of people will also report pain at the back of the head (53%), eyes (47%), and vertex (29%) [23].

Headaches developing after head trauma often possess the same characteristics as primary headache disorders [23]. In patients with PTHA 1 month after injury, migraine or probable migraine was the most common phenotype followed by tension-type headaches [6, 14, 15, 18, 19, 23] and cervicogenic headaches [7, 14, 23]. An even smaller subset of patients meet criteria for cluster headaches [4, 6, 7, 20, 23, 24], hemicrania continua [4, 6, 7, 24], chronic paroxysmal hemicrania [4, 6, 7, 24], or short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) [4, 6, 7]. Characterizing PTHA as a primary headache disorder is clinically relevant as treatment of PTHA is based upon the primary headache disorder it most closely resembles [6]. For example, PTHA resembling migraines are treated with therapies known to be effective for migraines. While characterizing headache type is often straightforward, it may be more challenging in certain patient populations. In a study with 95 active duty military personnel diagnosed with concussion referred for headache evaluation, 56.8% reported more than one headache type and 74.7% reported a continuous headache of any type present during all waking hours [37].

The major subgroups of headaches after trauma include tension-type headache, migraine, trigeminal autonomic cephalalgias, cranial neuralgias, cervicogenic headaches, and medication-overuse headache. Each of these is briefly described in the following paragraphs and outlined in Table 1.

Approximately 21–40% of PTHAs resemble tension-type headaches with a wide range seen in different studies [6, 7, 14]. Patients suffering

Table 1 Features of common types of headache syndromes after head trauma

Headache type	Laterality	Duration	Severity	Quality	Other symptoms	Comments
Migraine	Unilateral, asymmetric, or bilateral	4–72 hour	Moderate or severe	Often throbbing or pulsatile	Nausea or vomiting Photo/ phonosensitivity Aura Avoidance of physical activity	Patient may lie down in a dark, quiet place
Tension-type	Bilateral	30 minutes to several hours	Mild or moderate	Steady, squeezing	No nausea May have either light or sound sensitivity	Patient can usually function. OTCs often helpful
Occipital neuralgia	Unilateral	Continuous and/or brief episodes	Variable	Steady and/or "shooting"	Paresthesias in distribution of occipital nerve	Palpation over the occipital nerve reproduces pain
Cervicogenic	Unilateral or bilateral	Variable	Mild or moderate	Usually dull, steady, or "aching"	Neck pain, soreness, and/or stiffness HA triggered by neck movements or postures	Cervical muscle tenderness and/or spasm
Medication-overuse HA	Bilateral	Continuous	Mild or moderate	Usually steady	May have additional headaches characteristic of the underlying, original headache disorder that resulted in overuse	Use of analgesics >15 days/month. Headache often occurs after the analgesic has "worn off"

from tension-type PTHA will describe bilateral dull pressing pain of mild or moderate severity worsened by emotional stress and tension [23]. The pain is not aggravated by routine physical activity, light, or sound and is not associated with nausea or vomiting [1].

Approximately 38–62% of PTHAs resemble migraine [5–7, 14]. Migraine headaches are the most common form of PTHA after military-related concussion, with incidence ranging from 60% to 97% [7]. Patients suffering from migraine-type PTHA will describe unilateral throbbing or pounding pain that is moderate or severe [1, 6, 23], often with a piercing or drilling quality [23]. Migraine-type PTHAs are exacerbated by physical activity [1, 23] and accompanied by either nausea and vomiting or both light and sound sensitivity [1, 6, 23]. The headache attacks last several hours to several days without treatment [1]. Aura, a transient focal neurologic symptom that is most often visual in nature and precedes or accompanies the headache, occurs in a minority of patients with migraine and is not required for a headache to be considered a migraine [1]. The term "post-traumatic migraine" [17] is often used to describe PTHAs that would otherwise meet diagnostic criteria for migraine, although it is not listed as a diagnosis in ICHD-3 beta.

Head trauma can precipitate the development of trigeminal autonomic cephalalgias, but these are relatively rare presentations of PTHAs [4, 6, 7]. Trigeminal autonomic cephalalgias manifest as unilateral headache accompanied by lateralized and ipsilateral to the headache autonomic manifestations, such as conjunctival injection, lacrimation, ptosis, miosis, eyelid edema, rhinorrhea, or facial sweating abnormalities [1]. Specific subtypes of trigeminal autonomic cephalalgias include cluster headache, paroxysmal hemicrania, hemicrania continua, and SUNCT [1]. In a study of active duty military personnel with a diagnosis of concussion referred for headache management, 12.6% were found to have hemicrania continua [37].

Cranial neuralgias can result from head trauma [38, 39]. Occipital neuralgia is probably the most

common neuralgiform disorder following head or neck injury and typically presents with unilateral or bilateral paroxysmal lancinating pain in the posterior part of the scalp, in the distribution of the greater, lesser, or third occipital nerves radiating to the side of the head [1].

Trigeminal neuralgia and neuralgias involving the terminal branches of the trigeminal nerve, such as supraorbital neuralgia and infraorbital neuralgia, can also occur after head trauma [40, 41]. Compression, stretching, or other forms of injury to these peripheral nerves, their branches, or their central connections can alter synaptic transmission, initiating pain in the distribution of the affected nerve [42]. The pain is typically burning, stabbing, jabbing, or lancinating [41]. There may be severe brief paroxysms of pain that are superimposed on persistent, less severe pain in the distribution of the nerve. There is usually tenderness over the nerve, and there may be sensory impairment in the distribution of the nerve as well [41].

Approximately 4–10% of PTHAs resemble cervicogenic headaches [6, 7, 14]. Cervicogenic headaches are associated with cervical myofascial pain sources (myofascial trigger points) in the cervical spine, such as component bony, disk, and/or soft tissue elements [1]. Patients with this category of headaches usually have persistent or intermittent neck discomfort as part of their presentation [1]. Cervical range of motion may be reduced and pain may be exacerbated by provocative maneuvers, such as digital pressure on neck muscles. Cervicogenic headache is often located in the occipital area or posterior head region but may also affect anterior head regions. The head pain can be unilateral or bilateral.

Medication-overuse headache (MOH), sometimes called analgesic rebound headache, is an important contributor to chronic headaches following head trauma. Nineteen to 42% of patients with PTHAs develop this secondary headache disorder [43, 44]. A study found that 70% of adolescent patients suffering from persistent PTHAs met criteria for probable medication-overuse headache [45]. Medication-overuse headache develops in susceptible patients when frequent use of acute or symptomatic analgesic medication is continued over a prolonged period. Analgesic overuse is defined as regular use of acute or symptomatic analgesics (on 10 or more or, 15 or more days per month, depending on the medication) for more than 3 months [1]. Medication-overuse headache is typically bilateral, mild-to-moderate, and non-throbbing. The headache usually begins several hours after consuming the offending analgesic. The patient becomes trapped in a cycle of escalating headaches and increasing medication use. The diagnosis is confirmed when headaches improve after cessation of the overused analgesic [46, 47]. Typically, the headaches worsen for 1 or 2 weeks after analgesic cessation and then gradually improve over the next 4–6 weeks. MOH can be caused by frequent use of any analgesic, including nonsteroidal anti-inflammatory drugs (NSAIDS) [14, 18], ergotamines [46], and triptans [18, 46]. Medications that contain narcotics, butalbital, or benzodiazepines have a high risk to cause rebound headache and lead to abuse and habituation [18].

Differential Diagnosis

The vast majority of patients with PTHAs after concussion do not have an underlying, life-threatening condition. However, the clinician must ask the following question: "Are the headaches a harbinger of a serious underlying disorder that would significantly alter prognosis or require specific treatment?" Box 2 lists causes of headaches after head trauma. It is beyond the scope of this chapter to describe each of these disorders in detail. Clinicians who routinely evaluate patients after head trauma should be familiar with the key features of these disorders to avoid delays in diagnosis.

Box 2 Causes of headache after trauma

Dangerous causes of headache:
Cerebral vein or sinus thrombosis
Reversible cerebral vasoconstriction syndrome

Subdural or epidural hematoma
Intracerebral hemorrhage
Subarachnoid hemorrhage
Low or high intracranial pressure
Hydrocephalus
Carotid or vertebral artery dissection
Cavernous carotid fistula
Cerebral aneurysm
Skull fracture
Cervical vertebra fracture
Cervical disc protrusion
Primary headache disorders:
Migraine
Tension-type headache
Cluster headache
Others
Neuralgiform headaches:
Occipital neuralgia
Supraorbital or infraorbital neuralgia
Trigeminal neuralgia
Scalp laceration-associated neuralgia
Cervicogenic headaches:
Cervical myofascial pain
Cervical ligament strain
Cervical disc protrusion
C2–C3 facet joint dysfunction
Other causes:
Medication-overuse (rebound) headache
Medication side effect
Sinus injury
TMJ disorders
Post-craniotomy headache
Ocular pain (various causes)
Chemical meningitis
Headache due to a nontraumatic cause
Headache due to a psychiatric condition
Somatization
Malingering

There are a number of "danger signs" that should alert the clinician to the possibility of a potentially serious medical condition causing headaches [47, 48]. Danger signs include optic disc edema; drowsiness; confusion; memory impairment or loss of consciousness (LOC); paralysis; asymmetric pupillary response; progressive visual or neurologic changes; progressively worsening headache pattern; intractable headache; thunderclap headaches (rapid-onset headaches with maximal pain at the onset); headaches induced by position, Valsalva, or exertion; and systemic or constitutional symptoms, as well as new headache after 50 years of age [47, 48]. The SNOOP4 mnemonic (**S**ystemic symptoms; **N**eurologic symptoms; **O**nset, **O**lder, and **P**revious headache; **P**ostural or positional aggravation; **P**recipitated by Valsalva; **P**apilledema) is a simple tool that may be used to elicit headache danger signs or symptoms [49]. Headaches with atypical features can also be a sign of an underlying abnormality. Unfortunately, headaches fully resembling primary headaches can occur in patients with serious underlying medical conditions.

Clinical Evaluation

The major goals of the clinical evaluation are to exclude serious underlying etiologies, establish an accurate headache diagnosis, determine the impact of the headaches on the individual, and identify important comorbid conditions which may be perpetuating or exacerbating the headaches. This information is essential to formulating an effective therapeutic plan.

History

The history obtained from the patient is the most important part of the clinical evaluation and establishing whether a headache is primary or secondary in origin [47]. A detailed description of the headache should be obtained, including onset, location, quality, frequency, severity, duration, associated symptoms, triggers, functional impact, and changes in pattern over time [47]. If a patient is having difficulty recollecting certain headache details, encourage them to create a headache diary [47]. The specific characteristics of PTHAs can be used to classify them into categories that have treatment implications [6]. We find it useful to categorize PTHAs into those resembling migraine, tension-type headache, cervicogenic headache, trigeminal autonomic cephalalgia, neuralgiform headache, or probable MOH as described in the Clinical Features sec-

tion of this chapter. An individual patient may have more than one type of headache [37], so it is important to obtain a detailed description of each headache type. It is also important to ask about headaches that existed prior to the traumatic injury and whether there has been a marked change in the pattern of preexisting headaches.

Patients should be asked about the occurrence of focal neurologic symptoms [47], either during or between headache attacks, as well as other "danger signs" (see previous section). Post-traumatic migraines may be accompanied by an aura [24], which typically manifests as transient visual disturbance [47]. Other focal neurologic symptoms in patients with a history of head trauma should not be attributed to a migraine aura without first excluding other causes.

The clinician must ascertain all current and previously attempted headache therapies [47], including medications and non-pharmacologic treatments. The dose, effectiveness, tolerability, side effects, and duration of each therapy should be determined. This information is essential for determining whether a specific therapy has received an adequate trial and for identifying the presence of MOH [47]. Common pitfalls in headache treatment include prescribing nonoptimal medication doses [6], failing to treat with prophylactic agents for a sufficient period of time, and continuing to prescribe medications causing MOH [6]. Understanding the clinical response a patient had to specific medications can also have diagnostic utility. For example, headaches that are rapidly relieved by a triptan class medication are very likely to be migraines [6].

A number of standardized instruments can aid in the evaluation of patients with PTHAs. As previously mentioned, visual or verbal analog pain scales are useful for grading pain severity and tracking changes in pain over time. An instrument to measure headache-associated disability is highly recommended to better understand how the headaches are impacting the function of the patient. The Headache Impact Test-6 (HIT-6) [50, 51] and the Migraine Disability Assessment Scale (MIDAS) [51, 52] are two widely used disability scales, although neither one has been specifically validated in patients with PTHA [53, 54].

Patients with PTHAs often have concurrent medical and psychological conditions that can perpetuate or exacerbate headaches. Such conditions include insomnia, other sleep disorders [5], PTSD [7, 23], mood disorders [5], and chronic non-headache pain disorders [55]. These conditions should be screened for during the clinical evaluation. Standardized instruments can aid in detecting and monitoring comorbid conditions. Useful instruments include the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) [56], Hospital Anxiety and Depression Scale [57], and Minimal Insomnia Symptom Scale [58]. Box 3 summarizes the clinical evaluation of subacute and chronic headaches after head trauma.

Box 3 Clinical evaluation of subacute and chronic headaches after head trauma

History:
Severity and mechanism of trauma
Detailed description of headache(s) prior to and since head trauma
Onset
Location
Severity
Duration
Frequency
Quality
Triggers
Associated symptoms
Functional impact
Change in pattern over time
Current and past headache therapies
Doses
Duration of treatment
Side effects
Response to treatment
Other neurologic symptoms during or between headaches
Past and current medical problems
Social history including caffeine use and current stressors including legal issues
Family history of headaches
Physical exam:
Vital signs
Complete neurologic exam
Head and neck exam

Range of motion
Cervical muscle spasm
Trigger points
Cephalic or ocular bruits
Screening instruments:
Headache Impact Test (HIT-6)
Migraine Disability Assessment Scale (MIDAS)
Clinician-Administered PTSD Scale for DSM-5 (CAPS-5)
Hospital Anxiety and Depression Scale or PHQ-9
Neurobehavioral symptom inventory
Minimal Insomnia Symptom Scale
Imaging:
Review any prior imaging
Obtain imaging if "danger sign" (see text)
Use clinical judgment if no danger signs are present
Brain MRI ± MR angiogram
C-spine MRI ± MR angiogram

Physical Exam

Patients with headaches should undergo a careful neurologic examination, including vital signs and evaluation of mental status, cranial nerves, motor function, sensation, coordination, gait, and reflexes [59]. The vast majority of patients with headaches after mild head injury will not have focal or lateralizing motor, sensory, or reflex abnormalities. It is important to examine the optic discs for papilledema, the pupils for anisocoria, the eyelids for ptosis, and the eyes for chemosis, proptosis, or orbital edema [59]. Careful palpation for cranial, occipital, and cervical trigger points should be performed [59]. If the clinician is unable to adequately visualize the fundus for whatever reason, referral to an ophthalmologist for a dilated fundoscopic exam should be strongly considered [59].

Imaging

All patients with moderate or severe traumatic brain injury [60, 61], and many patients with concussion, should undergo a head CT during the acute evaluation. Head CT is recommended in the acute period for patients who lost consciousness and have one or more of the following features: headache, vomiting, age >60 years, drug or alcohol intoxication, short-term memory loss, physical evidence of trauma above the clavicle, post-traumatic seizure, GCS <15, focal neurologic deficit, or coagulopathy [60]. When patients present with subacute or chronic headaches following concussion, the clinician must decide whether neuroimaging is needed to exclude a potential underlying contributory abnormality. However, the yields of head CT and standard brain MRI are low in patients with a history of concussion [61]. Specific signs that suggest the need for neuroimaging in non-acute headache patients include abnormal neurologic examination findings [61], progressively worsening headache pattern [47], and headaches induced by position or Valsalva [47]. Headaches that fail to respond to an appropriate trial of therapy or possess atypical features not conforming to common headache phenotypes are additional indications for imaging.

MRI is more sensitive than CT and is the imaging study of choice in the subacute setting [60, 61]. In the acute setting, MRI may be considered in patients with normal CT scans but persistent unexplained neurologic findings [61]. The Defense and Veterans Brain Injury Center (DVBIC) recommends an MRI 72 hours after injury in any of the following situations: (1) sustained a concussion with alteration of consciousness (AOC) to include any memory loss greater than 15 minutes and has persisting or worsening symptoms after 72 hours, (2) sustained concussion with loss of consciousness (LOC) <30 minutes and has persisting or worsening symptoms after 72 hours despite a normal CT, (3) sustained three or more concussions in past 12 months, and (4) has a documented diagnosis of concussion and has a Military Acute Concussion Evaluation (MACE) Cognitive Score <25 after 72 hours post-injury [62]. DVBIC's recommendations on neuroimaging following concussion in the non-deployed setting include preferred and alternative MRI protocols for both 1.5 T and 3 T scanners [62].

MR or CT angiogram should be utilized in patients in whom arterial dissection [60], aneurysm [63], vasospasm [60], or carotid-cavernous fistula [64] are considerations. MR or CT venogram [65] should be performed in patients with possible cerebral vein thrombosis, a condition which can be triggered by trauma [65] and has variable manifestations, including headache [65], signs of elevated intracranial pressure [65], focal seizures [65], and/or focal neurologic symptoms. Cervical spine MRI may be utilized in patients with suspected cervicogenic headache to assess for structural abnormalities, such as herniated discs [66] or cervical nerve root impingement [66]; however, imaging is often of low yield as studies have not consistently shown differences in the appearance of cervical spine structures in patients suffering from cervicogenic headache [66, 67].

Other Diagnostic Studies

Lumbar puncture is rarely needed in the evaluation of PTHA. However, measuring the opening pressure is an important diagnostic tool for excluding low or high CSF pressure in selected cases. Patients with low CSF pressure headaches due to a dural tear, which can be caused by mild trauma, have head pain triggered by moving into an upright posture and relieved by lying back down [68]. CSF analysis may also be used to exclude infectious or inflammatory etiologies of headache in selected cases.

Treatment

The treatment of PTHAs can be both challenging and rewarding. To date, there have been no randomized, controlled clinical trials evaluating the efficacy of any therapies for PTHAs [6, 7, 69]. No treatments have been developed specifically for PTHA nor are there any US Food and Drug Administration (FDA) approved medications with this indication [69, 70]. Therefore, treatments that are known to be effective for primary headache disorders, such as migraine or tension-type headache, are typically employed.

Our approach to treating PTHAs based on headache type is outlined in Fig. 3. The acute phase of PTHA treatment begins with a history and physical examination to determine the severity of TBI and probe for danger signs before deciding on the need for neuroimaging. The goal of acute neuroimaging is to rule out intracranial hemorrhage, skull fracture, or vascular injury [69]. Immediately post-injury (0–72 hours) PTHA treatment focuses on rest and analgesic medications as needed [69]. Treatment days to weeks following injury is focused on aborting ongoing, recurrent headaches [69]. Treatment of PTHA weeks to 3 months post-injury involves following the algorithm outlined in Fig. 3, which focuses on recognizing the headache type with the goal of providing headache relief and preventing chronicity [69].

A systematic and rational approach to treatment is recommended. The major goals of treatment are to abort headache attacks, decrease headache frequency, and reduce disability. Comorbid conditions, allergies, or other drug sensitivities should be considered before every therapeutic decision [49]. Classification of the headache type is an important step in developing an individualized treatment plan. As discussed in the following sections and outlined in Fig. 3, a wide variety of pharmacologic and non-pharmacologic therapies can be utilized to optimize the outcome of different subtypes of PTHA. The DVBIC has published an expert, consensus guideline for treatment of military PTHA in deployed and non-deployed settings [49].

Abortive Medications

Abortive headache treatments provide acute relief of individual attacks of headache. The goal is to achieve complete relief or nearly complete relief of head pain as rapidly as possible so that the patient can resume normal activities. A practical goal is to achieve headache relief within 2 hours of pain onset.

NSAIDs are a good first choice for most types of PTHAs (Fig. 3). NSAIDs are effective for migraine [71], tension-type headache [72],

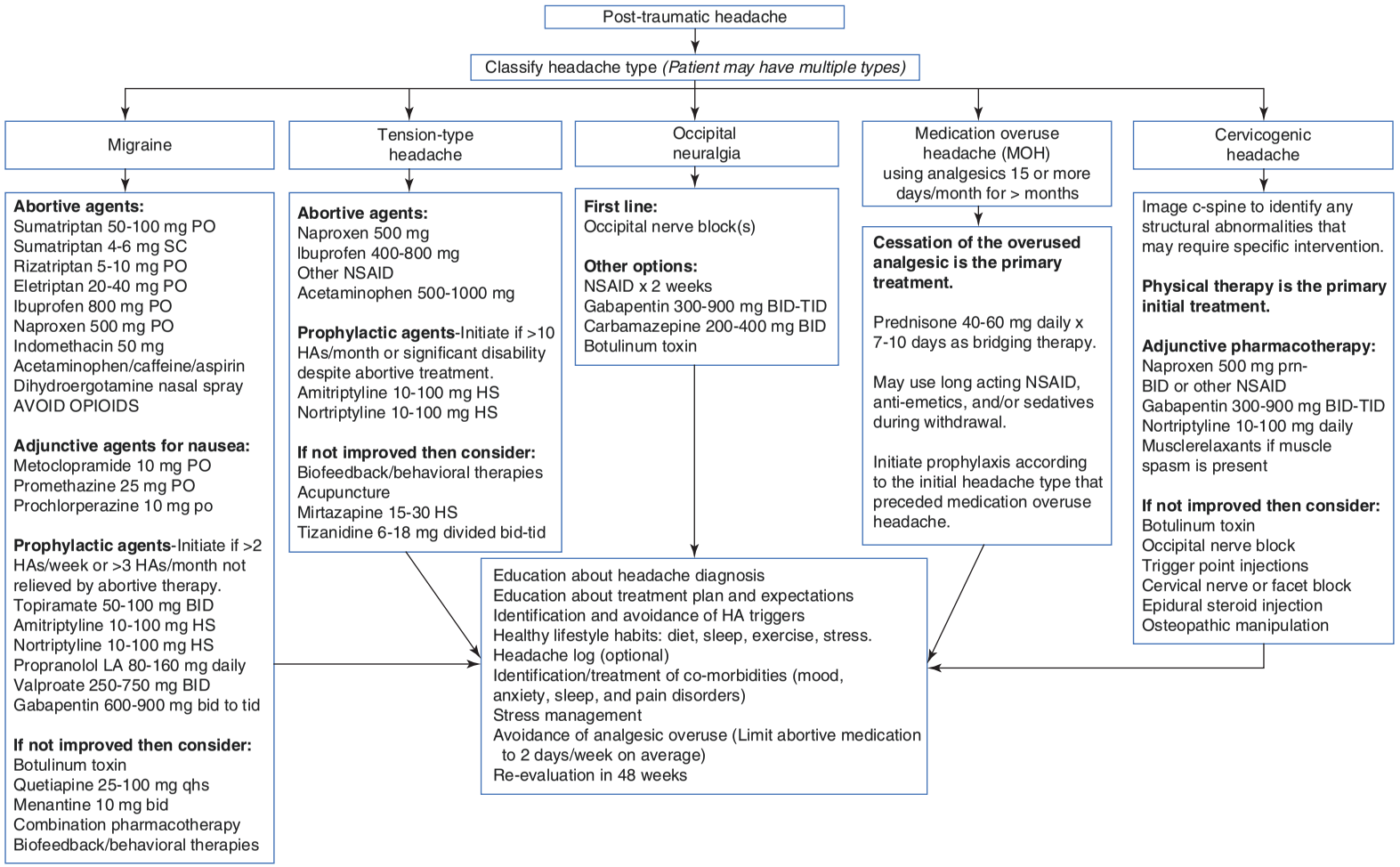

Fig. 3 Treatment pathway

and cervicogenic headache [73]. The specific NSAID agent is not especially important, although naproxen [71] and ibuprofen [51, 74] are the most widely used in the United States. Ketorolac injection may be helpful for those who cannot take, or do not respond to, oral medications [74, 75].

Caution should be exercised when using NSAIDs within 24 hours of injury, especially for moderate and severe TBIs, since NSAIDs increase bleeding time and can, therefore, increase the possibility of bleeding and cause surgical complications should surgery be required [6].

The triptan class of medications should be tried in patients with migraine-type PTHAs that fail to respond adequately to NSAIDs (Fig. 3) [6]. Triptans are serotonin-1B/1D agonists that are FDA-approved for the treatment of acute migraine [6]. Binding to serotonin-1B receptors causes vasoconstriction, and binding to serotonin-1D receptors inhibits the release of inflammatory peptides, such as calcitonin gene-related peptide causing an anti-inflammatory effect [6]. Uncontrolled studies suggest that these agents are effective for aborting attacks of PTHA [7, 14, 20, 76]. There are more than half a dozen [74, 77] triptan agents on the market, and there are several different routes of administration [78]. Oral triptan agents are effective for the majority of patients with migraine [78]. Patients who have rapid-onset headaches or who develop severe nausea or vomiting early in the headache attack may benefit from a nasal or subcutaneous route of administration [79]. Triptans have an excellent safety record [80], although, because of their vasoconstrictive properties, they are contraindicated in patients with significant risk factors for vascular disease and those with central, coronary, or peripheral vascular disease [6]. Patients who experience nausea or vomiting during acute migraine attacks should be prescribed an antiemetic agent [74], such as metoclopramide or promethazine (Fig. 3). Triptan agents may be given in combination with a NSAID for enhanced effectiveness [81].

There are a variety of combination analgesic products that are marketed for acute treatment of headaches. Such combination capsules include butalbital-acetaminophen-caffeine, butalbital-aspirin-caffeine, acetaminophen-dichloralphenazone-isometheptene, and aspirin-acetaminophen-caffeine. These products may be helpful for patients with infrequent attacks of mild-to-moderate migraine headache pain. Aspirin-acetaminophen-caffeine capsules have evidence supporting their effectiveness in migraine [51], but the other agents have not been rigorously tested [82, 83]. Anecdotally, these agents do not seem to be highly effective for CPTHAs and often lead to overuse and dependence. Butalbital, a barbiturate, can cause sedation and dependence, and should be avoided in treatment of PTHA [82, 83]. Dichloralphenazone has mild sedating properties [84]. Many of these products contain acetaminophen, which can reach hepatotoxic levels if the patient uses multiple doses or takes other acetaminophen-containing products. All of these products are relatively short-acting, and many patients require repeated doses. These properties may contribute to the risk of developing rebound headache with these agents. Patients using these medications must, therefore, be educated about their potentially addictive properties and the risk of developing MOH [46, 83]. We do not consider these products first-line treatments for PTHAs and avoid using them in patients who have two or more headaches per week because of the risk of developing rebound headaches.

Opioid medications are generally not highly effective for most headache types and should not be used as first-line headache abortive agents [49, 82]. Opioids should be avoided as much as possible in patients with CPTHAs as opioid use is associated with a greater risk of developing chronic daily headache.

Treatment of MOH requires cessation of the causative analgesic agent [49, 85]. Sudden cessation of the offending agent can usually be accomplished, although patients taking large amounts of butalbital-containing products should be tapered gradually to prevent drug-withdrawal seizures [85, 86]. Likewise, patients on large doses of opioids and benzodiazepines may need to be tapered down or monitored to prevent severe withdrawal symptoms [85]. Cessation of analgesic medication inevitably results in worsening

daily headaches for about 2–10 days, but can persist for up to 4 weeks, followed by a gradual improvement back to an episodic headache pattern [85]. Patients must understand that withdrawal headaches are expected for at least 2 weeks and must be fully committed to the treatment plan. Varying doses of prednisone from 60 to 100 mg have been used for 5 or more days [87, 88] in the treatment of MOH with some studies indicating that prednisone decreases the use of other rescue medications rather than actually decreasing the number of headaches or headache hours [89]. Another study compared celecoxib against prednisone in treating patients with MOH and found that while neither medication reduced headache days or rescue medication requirements, celecoxib (400 mg/day for 5 days after which dose was tapered by 100 mg/week) decreased headache severity better than prednisone [88]. Naproxen and other NSAIDs, such as indomethacin and ketorolac, are effective rescue medications while patients are undergoing treatment for MOH [89]. A triptan (sumatriptan [85, 90], eletriptan [90], or frovatriptan [90]) may be used sparingly for severe exacerbations. Sleep-inducing medication [91], antiemetic medications [87, 91], and adequate hydration [87] may be helpful during the withdrawal period.

Headache Prevention Medications

Patients who experience frequent headaches may benefit from daily use of headache prophylactic medication. Because most patients with PTHAs experience spontaneous resolution in the first few weeks after injury, many practitioners do not initiate prophylactic therapy until some period of time has passed. It remains to be determined whether initiation of headache prophylactic therapy in the first few days or weeks after injury mitigates acute PTHAs or decreases the likelihood of developing CPTHAs. At this time, there is insufficient evidence to guide the decision as to when after the injury headache prophylaxis should be started. However, most practitioners would agree that patients who continue to experience frequent headaches more than 2 months after the injury are appropriate candidates for prophylactic therapy.

In general, patients who experience six headache days a month with at least four headache days associated with moderate impairment or at least three headache days with severe impairment or requiring bed rest, over a period of several months despite use of abortive medications, are good candidates for headache prophylactic medication [92, 93].

A practical treatment goal of prophylactic medication is a 50% or greater reduction in headache attack frequency within 3 months [94, 95]. Prophylactic medications require a minimum of 2 months to take effect [93]. They should be started at a low dose [6, 93, 95] to minimize side effects and gradually increased over weeks or even months [95] until the frequency of headaches decreases, side effects develop, or the highest target dose is reached. Patience on the part of both the patient and provider is critical. Switching prophylactic agents prematurely, without first titrating up the dose or treating for a minimum of 2 months, is a common mistake that should be avoided.

There are no randomized, controlled trials of prophylactic medications for PTHAs. Agents known to be effective for primary headache disorders are used to treat patients with PTHAs. Studies specifically looking at prophylactic medication in the setting of PTHA have evaluated propranolol, amitriptyline, and valproate, and each was found to have statistically significant efficacy [18]. A retrospective cohort study involving 170 US soldiers diagnosed with persistent PTHA found topiramate (100 mg/day in divided doses) to be superior to low-dose tricyclic antidepressants (TCAs) (25–50 mg/day) at reducing headache frequency [76]. Selection of the prophylactic agent is based primarily on the specific headache type (Fig. 3). The four oral agents approved by the FDA for the prevention of migraine are the beta-adrenergic blocking agents propranolol (tablets and liquid) and timolol (tablets) and the anticonvulsants divalproex sodium or sodium valproate (tablets) and topiramate (tablets) [96].

Other medications that can be useful for migraine prevention include amitriptyline, nortriptyline, gabapentin, and calcium channel

blockers [94, 97, 98]. In clinical practice, if PTHAs have migraine features (i.e., post-traumatic migraine), then a prophylactic agent known to be effective for migraine should be tried (Fig. 3) [6]. Selection of a migraine prophylactic agent is influenced by the patient's comorbid conditions. One should try to avoid prophylactic agents that will aggravate comorbid conditions and select an agent that may benefit one or more comorbid conditions. Propranolol, or another beta-blocker, is a good choice for patients with post-traumatic migraine who also have hypertension [98] or essential tremor [99]. Topiramate is optimal for patients with migraine with comorbid obesity or epilepsy [98]. Valproate is appropriate for post-traumatic migraines in the setting of comorbid bipolar disorder or epilepsy but must be used with caution owing to its teratogenicity, risk of hepatotoxicity, and propensity for promoting weight gain [98].

TCAs, such as amitriptyline or nortriptyline, are appropriate first-line agents for prophylaxis of PTHAs resembling tension-type headaches [72, 100]. TCAs have evidence for efficacy in tension-type headache though are unproven for PTHAs. Muscle relaxants have no proven benefit for tension-type headache [100]. Other prophylactic agents that may be helpful for tension-type headache are tizanidine, baclofen, venlafaxine, and mirtazapine [100]. Post-traumatic neuralgiform headaches, such as occipital neuralgia or trigeminal neuralgia, may benefit from anticonvulsant therapy. Carbamazepine is the most established agent for trigeminal neuralgia [101]. Oxcarbazepine is also effective for trigeminal neuralgia with a better side effect profile than carbamazepine but with less flexibility in dose titration [101]. Phenytoin, baclofen, or clonazepam can be considered as alternative or add-on medications when necessary [101]. Gabapentin can be used to treat occipital neuralgia (Fig. 3) [101]. Lamotrigine is another option for neuralgiform headaches as it is well tolerated and has minimal adverse cognitive side effects but must be slowly titrated up to minimize the risk of a serious mucocutaneous reactions (rash or Stevens-Johnson syndrome) [101].

Non-pharmacologic Therapies

A variety of non-pharmacologic interventions may be helpful in treating PTHAs. Such treatments include behavioral therapies, physical modalities, and injection procedures. There are no randomized, controlled trials evaluating the effectiveness of any of these approaches for PTHAs, but there is evidence supporting their use in other headache disorders. Most non-pharmacologic techniques have minimal-to-no adverse effects and may be used as an adjunct to pharmacologic treatments.

All patients with PTHAs should receive education about their diagnosis and treatment plan. Patients with acute PTHAs should be reassured that their headaches are likely to improve over time. Patients with CPTHAs should be informed that there are numerous therapies that may alleviate headaches, but it may take multiple trials to optimize treatment. Patients should be given clear instructions about the goals and proper uses of any prescribed medications. Establishing realistic expectations and enlisting the active participation of the patient will improve compliance.

Lifestyle modification is a simple, yet often overlooked, technique [96]. Patients should be encouraged to establish healthy meal, sleep, and exercise patterns [49]. Patients may identify specific triggers for their headaches which can be avoided. Caffeine overuse, smoking, and alcohol use can contribute to headaches [49]. A headache log may help identify potential triggers in some cases.

Several uncontrolled studies of education, relaxation therapy, and biofeedback have shown favorable results in PTHA [38]. These techniques seem to be especially helpful for patients with PTHAs who have significant muscle tightness, anxiety, or insomnia. Relaxation training, thermal biofeedback combined with relaxation training, EMG biofeedback, and cognitive-behavioral therapy are considered treatment options in the prevention of migraine [102].

Physical modalities, such as physical therapy, osteopathic manipulation therapy, acupuncture [49], and massage, have not been evaluated for PTHA [103]. These techniques may be useful as adjuncts to medical therapy, particularly in

patients where headache symptoms can be reproduced with palpation of cervical muscles, suboccipital muscles, or over the temporalis muscle region (Fig. 3) [103]. Physical therapy is an important initial step in treating post-traumatic cervicogenic headache. Physiotherapy, including joint mobilization, range of motion, cervical traction, soft tissue massage, myofascial release, muscle strengthening, and posture/body mechanics adjustments, should be considered in the treatment of cervicogenic headache [73].

Procedures

Patients with headaches secondary to cervical pathology often benefit from trigger point injections, epidural injections, and facet blocks. Common nerves blocked for headache treatment include the greater occipital nerve (GON), lesser occipital nerve (LON), auriculotemporal nerve (ATN), supraorbital nerve (SON), supratrochlear nerve (STN), and sphenopalatine ganglion (SPG) [103]. Typically, these sites are injected with an anesthetic such as bupivacaine (0.25 to 0.75%) or lidocaine (2%), with volumes ranging from 0.5 to 2 mL per site [103].

Peripheral nerve block, with the greater occipital nerve being the most commonly blocked site, for the treatment of PTHA has been evaluated and published in a few case reports, but no randomized double-blind placebo-controlled studies exist [103]. Many of these studies focused on pediatric patients; however, 1 retrospective series included 87 adult patients with PTHA, with 72% of patients reporting improvement up to 6 months following GON block with lidocaine and methylprednisolone [103].

Trigger point injections require identifying locations where palpation causes maximal and referred pain. These points include but are not limited to the occipitalis, frontalis, masseter, temporalis, trapezius, levator scapulae, semispinalis capitis, splenius (cervical and suboccipital regions), sternocleidomastoid, and longissimus capitis muscles [103]. Multiple sites are injected with 1–2 mL of anesthetic agent and steroid using a 0.5- to 1-inch needle [103]. Trigger point injections have not been studied for PTHA but have been shown to improve cervicogenic headache [103].

Onabotulinum toxin type A (Botox/BTX) is FDA-approved for the treatment of chronic migraine [96, 103]. The efficacy of BTX in PTHA has been reported in individual case reports [103–106]. A retrospective consecutive case series conducted at Womack Army Medical Center in Fort Bragg, North Carolina, included 63 patients, all of whom were male, serving on active duty, with a mean age of 31 and a diagnosis of CPTHA [104]. All patients received at least 1 treatment of BTX with a majority receiving the current FDA-approved protocol of 31 fixed site injections (5 units per site) [104]. Based upon patient reports and records, treatment response was determined using a global evaluation of change (GEC) coded to better, no difference, or worse. GEC was improved in 41 (64.1%), unchanged for 18 (28.5%), and worse for 2 (3.2%), with no data available for 3 (4.7%) lost to follow-up after the initial injection [104]. Further prospective studies of BTX injections, thus, are needed before this medication can be routinely recommended for use in PTHA.

Peripheral nerve stimulation and surgery may be considered in patients with refractory headache. There is no widely accepted definition for refractory headache; however, the American Headache Society and European Headache Federation have proposed definitions based on the failure of preventative medications [103]. Other groups require a failure of an adequate trial of multiple oral preventative medications, combination nerve blocks, at least 5 days of inpatient treatment, and BTX injections on three occasions, prior to classifying a headache as refractory [103]. Peripheral neurostimulation involves placing leads over peripheral nerves located in the head. A random subgroup analysis of 163 patients with dual GON and SON stimulators reported, on average, a 73% decrease in headache days [103]. Trigger site deactivation surgery can be performed at frontal, temporal, occipital, and sinus regions, based on the location of the headache. Patients are selected based on their response to BTX injections and the initial placebo-controlled trial involved 76 patients, 28 of whom

reported headache resolution at 1 year and 41 of whom reported headache improvement [103]. Studies are needed to validate the usefulness of these more invasive techniques before they can be routinely recommended for use in PTHA.

Treatment of Comorbid Conditions

Treating headaches in isolation, without taking into account comorbid conditions, can contribute to treatment failure. Identifying and treating concurrent conditions are important steps in optimizing the headache care plan. Comorbid conditions may limit treatment options or provide therapeutic opportunities. One should avoid headache treatments that may exacerbate comorbid conditions and select headache treatments that benefit one or more comorbid conditions. Comorbid conditions with PTHA that may influence selection of headache prophylactic medication include concurrent primary headache disorders, sleep disorders, asthma and allergic rhinitis, epilepsy, hypertension, alcohol abuse, depression, anxiety, PTSD, obesity, analgesic overuse, postamputation limb pain, and other chronic pain disorders [96].

A retrospective cohort study among 270 US Army soldiers diagnosed with PTHA found that 39% of participants screened positive for PTSD, which was defined as a score ≥ 50 on the PTSD Symptom Checklist (PCL) [31]. The authors found depression symptoms, as measured by the Patient Health Questionnaire (PHQ)–9 instrument, were significantly more prevalent in participants with PTSD (60% with PTSD vs. 7.8% without PTSD; $p < 0.01$) [31]. Patients with PTSD did not have increased headache frequency or a less favorable response to prophylactic therapy [31]. This finding was at odds with previous reports of a strong association between PTSD and chronic daily headaches [31]. The authors noted that patients with a diagnosis of PTSD were referred to behavioral health, which may suggest that treatment of comorbid PTSD, in addition to headache prophylaxis, is beneficial to the prognosis of PTHA [31]. Patients with psychological or psychiatric conditions should be evaluated and treated for these conditions, ideally by a mental health professional.

Summary

PTHAs are a heterogeneous syndrome that can be challenging and rewarding to treat. PTHAs are currently defined as headaches, with any features, that begin within 7 days of injury or within 7 days of regaining consciousness following trauma or injury to the head and/or neck. Such headaches often resolve in the first few months after injury, but chronic headaches can persist for years. A comprehensive diagnostic and therapeutic approach is needed to establish an individualized treatment plan that addresses all of the potential underlying causes of head pain as well as comorbid conditions that can perpetuate the headache syndrome. PTHAs often resemble primary headache disorders and are treated in a similar manner. Classifying the phenotype of PTHA helps guide treatment. A combination of pharmacologic and non-pharmacologic interventions may be necessary to achieve a favorable outcome. Studies are needed to identify the biological mechanisms that generate PTHAs and to determine the most effective therapies.

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Epileptic and Nonepileptic Seizures after Traumatic Brain Injury

Katherine Hamilton and Karen Parko

Introduction

Since ancient times, traumatic brain injury (TBI) has been associated with the development of epilepsy. In *"Injuries of the Head,"* Hippocrates (460–357 BC) recognized that a wound to the left temporal region could cause convulsions of the right side of the body [1]. Physicians of the same era also came to recognize these posttraumatic seizures as a poor prognostic sign. More detailed descriptions of traumatic brain injuries resulting in seizures can be found during the Renaissance. However, posttraumatic epilepsy (PTE) remained largely underappreciated until the late nineteenth century. For instance, in a series of 67 patients described by French physician Leuret in 1843, epilepsy was believed to arise from a head injury in just one case, while "fear" was the most common etiology, responsible for 35 cases [2].

TBI is increasingly common in the United States, accounting for a staggering 2.5 million emergency department visits, 280,000 hospitalizations, and 50,000 deaths each year with a 70% increase in rates of TBI-related Emergency Room visits over the past decade [3]. Given the recognition of military blast exposure as a "signature injury" of recent warfare [4, 5] and the proliferation of firearms worldwide [6], rates of TBI will likely continue to increase. TBI is now widely recognized as an important etiologic consideration in the epilepsy population, as it accounts for 5% of all epilepsy in the general population and 20% of acquired or symptomatic epilepsy [7, 8]. PTE is the most common cause of new-onset epilepsy in young adults [2], and in military populations the probability of developing PTE can exceed 50% after penetrating brain injury [9]. Although PTE has become more readily recognized and studied, it has proven extremely difficult to treat both medically and surgically, requiring increased focus on this topic.

In this chapter we will:

1. Review the varied *definitions* classifying posttraumatic seizures and severity of brain injuries.
2. Discuss the *epidemiology and risk factors* for PTE in both general and military populations.
3. Summarize recent *literature* demonstrating that TBI, especially mild TBI, is associated with development of psychogenic nonepileptic seizures (PNES).
4. Examine the *types* of seizures in PTE and the *timing* of the onset of seizures.
5. Outline potential *diagnostic* tools.
6. Review the *treatment* of posttraumatic seizures and epilepsy.
7. Look at the impact of PTE on patient *outcomes.*

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8. Explore the *pathophysiology* of PTE.
9. Conclude with an update on PTE as a model of *epileptogenesis,* animal models and biomarkers of PTE, and novel therapeutic strategies.

Definitions

PTE is a somewhat heterogeneous condition, and one of the major challenges in studying PTE and interpreting existing data is recognizing the various definitions that are employed. Seizure after head trauma can first be classified according to the time interval between events. The following definitions are widely accepted:

- *Immediate seizures:* occurring less than 24 hours after injury.
- *Early seizures:* occurring between 24 hours and seven days after injury.
- *Late seizures:* occurring more than seven days after injury.

Most investigators have defined PTE as the occurrence of one or more unprovoked *late* seizures after head injury. Immediate and early seizures are believed to be the result of acute injury and do not constitute epilepsy.

The other main set of definitions to consider involves rating the severity of head injury. The most widely accepted definitions characterize head injuries into the following three severities:

- *Mild:* Glasgow Coma Scale (GCS) score 13–15, alteration in consciousness ≤24 hours, loss of consciousness <30 minutes, posttraumatic amnesia ≤24 hours, and negative cerebral imaging.
- *Moderate:* GCS score 9–12, alteration in consciousness >24 hours, loss of consciousness between 30 minutes and 24 hours, posttraumatic amnesia between 24 hours and 7 days, and either positive or negative cerebral imaging.
- *Severe:* GCS score 3–8, alteration in consciousness >24 hours, loss of consciousness ≥24 hours, posttraumatic amnesia ≥7 days, and positive cerebral imaging.

Within these definitions, positive cerebral imaging is mainly defined as the presence of a skull fracture, cerebral contusion, or intracranial hemorrhage of any type.

While the main focus of this book is mild TBI, unfortunately less is known about mild TBI and the development of PTE compared to severe injury. This may be a manifestation of mild TBI patients not coming to medical attention. In addition, within the military there existed a stigma against reporting mild head injuries. This chapter will highlight each instance in which studies have addressed mild TBI; however, we will also spend considerable time discussing moderate and severe TBI.

Epidemiology and Risk Factors

The risk of developing epilepsy following common brain injuries depends heavily on the severity of the injury [10–12]. Figure 1, adapted from Dr. Susan Herman's 2002 article in *Neurology,* summarizes these relative risks and clearly illustrates the strong relationship between the severity of head injury and the risk of developing PTE. In general, risk factors with a relative risk greater than 10 are believed to have a strong causal relationship, while those with a relative risk of 4–10 have a probable causal relationship [13]. Severe TBI confers a relative risk up to 29 times that of the general population, placing it behind only brain tumors and subarachnoid hemorrhage [13]. Moderate and mild TBIs are much less likely to lead to PTE based on population-based studies [11], although recent studies suggest that even mild TBI leads to increased risk [14–16].

Below we review the seminal studies examining incidence of PTE, which notably are quite heterogeneous in both their definitions and methodology. For the purposes of this discussion, we will separate these studies by the population examined – civilian versus military and population-based versus patients admitted to a medical facility – as these groups vary significantly. For each study, we will consider the employed definition of head injuries, reported

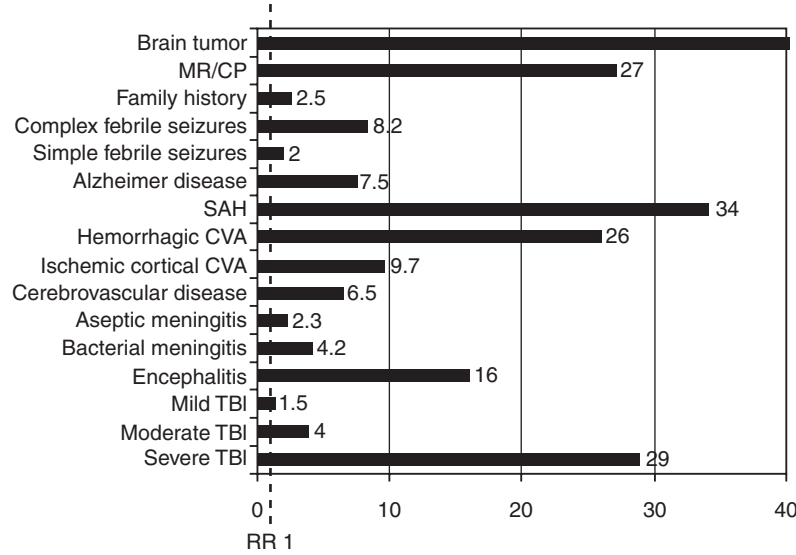


Fig. 1 Relative risk for unprovoked seizures after common brain injuries. The dotted vertical line represents the general population risk for unprovoked seizures. (*MR/CP* mental retardation/cerebral palsy, *SAH* subarachnoid hemorrhage, *CVA* cerebrovascular accident, *TBI* traumatic brain injury. (Used with permission of Wolters Kluwer from Herman et al. [13]))

incidence of early and/or late seizures, and the respective risk factors identified for development of PTE.

Population-Based Studies

There have been several large studies examining the incidence of PTE in the civilian population. Most recently, Mahler and colleagues [15] conducted a population-based case-control study using a national Swedish registry to compare relative risk of seizure following TBI in 1885 people with first-time unprovoked seizures versus 15,080 matched controls without TBI. History of TBI was determined based on ICD hospital discharge diagnoses of skull fracture, mild TBI/concussion, and severe TBI (further subdivided into parenchymal hemorrhage versus nonparenchymal hemorrhage). Relative risk of unprovoked seizure was increased among patients with all types of head injuries except for isolated skull fracture and was higher with more severe forms of TBI. For example, mild TBI doubled the risk of seizure (RR 2.0, 95% CI 1.5-2.7), whereas a combination of brain contusion and intracerebral hemorrhage had a relative risk of 42.6 (95% CI 12.2-148.5). Although the risk was highest within the first six months after both severe and mild TBI, it was still increased >10 years after all subtypes of TBI. Interestingly, while there was no gender difference in risk of PTE after severe TBI, there was a trend toward women having a higher risk for seizure after mild TBI compared to men (RR 24 vs. 1.9).

Another large population-based study was performed by Christensen and colleagues [14] in 2009, in which they reviewed records of 1,605,216 people born in Denmark during the period 1977–2002 from a national registry and reviewed risk of epilepsy in patients sustaining TBI (78,572 persons). Mild brain injury (concussion) was defined as direct head trauma manifesting with changed brain function without loss of consciousness greater than 30 minutes, GCS less than 13, or traumatic amnesia lasting longer than 24 hours. Similar to findings of Mahler and colleagues [15], the risk of PTE was two times higher after mild brain injury (RR 2.22, 95% CI 2.07-2.38) and continued to be elevated even more than 10 years after injury (RR 1.51, 1.25-1.85). In comparison, severe TBI was associated with a 7.4 relative risk (95% CI 6.16-8.89) of epilepsy and skull fracture with a 2.17 relative risk (1.73-2.71). The authors also discovered that relative risk of PTE after mild and severe TBI increased with age and was especially high among persons older than 15 years of age. Also similar to findings in the Swedish population, the risk of PTE was slightly higher among women

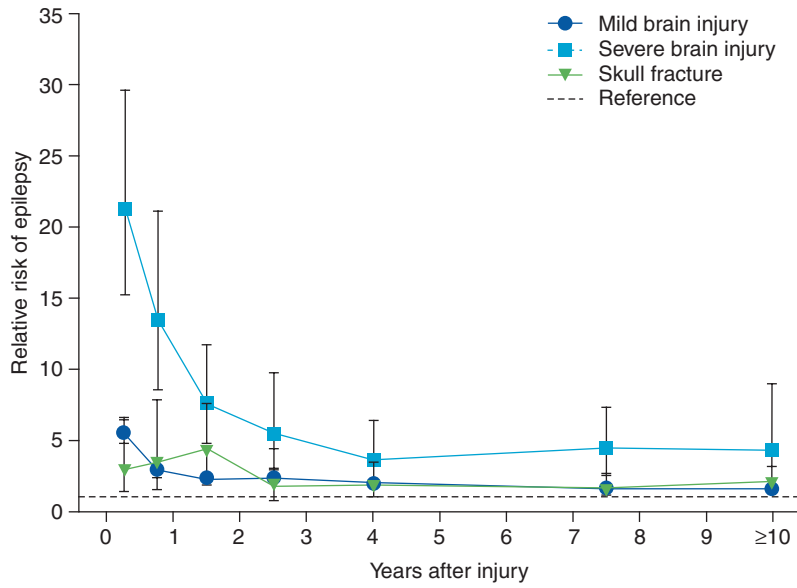
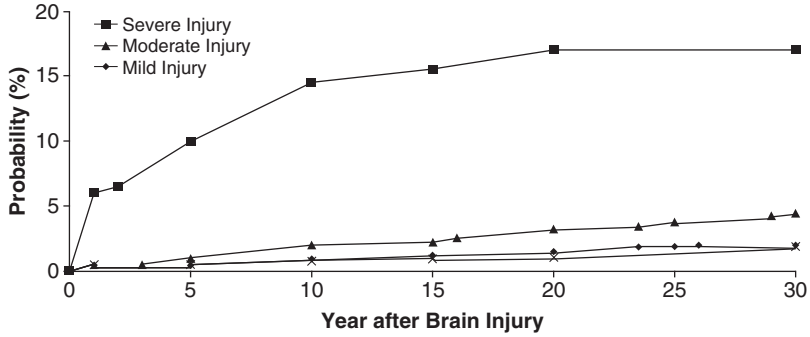


Fig. 2 Relative risk of epilepsy after brain injury in Denmark (1977–2002) shows increased risk after mild TBI even after 10 years. (Used with permission of Elsevier from Christensen et al. [14])

compared to men sustaining mild TBI (RR 2.49 vs. 2.01, $p = 0.003$), suggesting that women may be more susceptible to seizures after minor head injury. Both the Swedish and Danish population studies importantly demonstrated that while risk of PTE was highest among persons with severe head injuries, mild TBI also led to a substantial risk over a fairly long time period, as illustrated in Fig. 2.

Another study from Taiwan retrospectively reviewed records of 19,336 TBI patients and 540,322 non-TBI patients older than 15 years old from 2000 to 2008 using Taiwan's National Health Insurance Research Database. Compared with the non-TBI cohort, adjusted hazard ratio (HR) for development of epilepsy among people with mild head injury was statistically significantly higher (HR 3.02, 95% CI 2.42-3.77), although again, severe TBI and skull fracture were associated with an even higher risk – HR 5.05 (95% CI 4.04-5.79) and 10.6 (95% CI 7.14-15.8), respectively. This study defined mild brain injury as concussion without structural damage, while severe brain injury must have involved structural brain injury including brain contusion, subdural, epidural, subarachnoid, or intracranial hemorrhage. Patients with mixed types of cerebral hemorrhage were at the highest risk of epilepsy compared to the non-TBI cohort, and in this study, men had a 1.47 higher risk of epilepsy compared to women [17].

In the United States, Annegers and coauthors [18] have published two older population-based studies. Their 1980 study followed a cohort of 2747 civilians in Rochester, Minnesota, over a total of 28,176 person-years. There were 1640 mild head injuries defined as either unconsciousness or posttraumatic amnesia for less than 30 minutes without evidence of a skull fracture. The 912 moderate head injuries were defined by skull fractures or loss of consciousness or posttraumatic amnesia for more than 30 minutes. Severe head injuries, of which there were 195, had at least one of the following features: brain contusion (diagnosed by abnormal neurologic exam or by observation during surgery), intracranial hematoma, or more than 24 hours of either unconsciousness or posttraumatic amnesia. Early seizures were defined as occurring "while still suffering from the direct effects of the head injury," up to 2 weeks after injury. Early seizures were observed in 2.1% with the main risk factors being age <15 years and severe head injury. Late, unprovoked seizures occurred in 1.9% with the main risk factors being severe head injury and the presence of early seizures. Broken down by severity, the risk of PTE was 7.1% within 1 year of severe TBI and 11.5% within 5 years. For



No. of Patients				
Mild injury	2758	1751	1191	609
Moderate injury	1455	934	660	351
Severe injury	328	181	136	74
Total	4541	2866	1987	1034

Fig. 3 Cumulative probability of unprovoked seizures in 4541 patients with traumatic brain injuries according to the severity of the injury and the incidence of seizures in the general population. The cumulative incidence in the population was derived from incidence rates, with the use of the density method to convert the rate to risk estimates. The asterisks indicate the incidence in the general population at specific points in time. (Used with permission of Massachusetts Medical Society from Annegers et al. [11])

moderate head injuries, the risks were 0.7% and 1.6%, respectively, and for mild head injuries, 0.1% and 0.6%, respectively. As such, the authors concluded that the risk of PTE following a mild head injury was no greater than the risk experienced by the general population.

Utilizing the same definitions as the previous study, Annegers and coauthors [11] published a second population-based study in 1998. This cohort was comprised of 4541 children and adults living in Olmsted County, Minnesota, and was followed for 53,222 person-years. Figure 3 depicts the cumulative probability of seizures based on severity of injury compared to the general population. They found a significantly elevated risk of PTE among severe and moderate head injuries, as evidenced by the following standardized incidence ratios: 17.0 (CI, 12.3-23.6), 2.9 (1.9-4.1), and 1.5 (1-2.2) for severe, moderate, and mild head injuries, respectively. When looking specifically at mild head injuries, the increased risk of seizures abated after 5 years, after which the risk of epilepsy was no greater than the risk incurred by the general population. When considering severe head injuries, they noted a significantly increased risk of seizures more than 10 years after injury. Finally, employing a multivariate model of analysis, the authors demonstrated an increased risk of late seizures, or PTE, with severe injury, brain contusion or hematoma, loss of consciousness or posttraumatic amnesia for >24 hours, and an age of 65 years or older.

Studies of Hospitalized Patients

A somewhat more heterogeneous group of studies exists examining the incidence of seizures in TBI patients admitted to the hospital or a TBI rehabilitation center. Not surprisingly, the rate of early and late posttraumatic seizures is higher in these studies compared to the nonhospitalized population-based studies.

- Briefly, one study followed 896 consecutive patients admitted to the hospital and calculated incidences of 4.2% and 10.2% for early and late seizures, respectively [19]. Of note, late epilepsy was defined as "one or more late fits," and prophylactic phenobarbitone was prescribed for patients who were deemed likely to develop epilepsy. Early seizures were more likely in patients with >24 hours of posttraumatic amnesia, depressed skull fracture, and intracranial hematoma. The risk of late seizures was

increased by intracranial hematoma alone and a combination of depressed skull fracture and >24 hours of posttraumatic amnesia.

- A second study followed 137 consecutive head injury patients admitted to the hospital for a median of 12 months [20]. The incidence of late seizures was 13.1%, and the risk of PTE was increased by low GCS [3–8], presence of a single lesion on CT (particularly temporal or frontal), the presence of early seizures (defined as occurring within 4 weeks of injury), and the development of a focal EEG abnormality one month after injury.
- Englander and coauthors [21] investigated the rate of PTE among 647 TBI patients admitted to four trauma centers. The study preselected for moderate and severe head injuries by including only those patients with a positive CT scan within 7 days of injury or a best GCS score of ≤10 in the first 24 hours post-injury. Late posttraumatic seizures, defined as occurring more than one week after injury, occurred in 10.2% of the population. Of note, many of the patients were initially treated with prophylactic phenytoin; however, to remain in the study, phenytoin had to have been discontinued by week four. The investigators found an increased risk of seizures associated with multiple or bilateral contusions, dural penetration, the need for multiple intracranial surgeries, subdural hematoma requiring evacuation, and midline shift greater than 5 mm. Interestingly, the investigators found that the probability of unprovoked seizures at 2 years was related to the number of cerebral contusions, with approximately 25% probability for patients with multiple contusions, 8% for a single contusion, and 6% for no contusions.
- One final study evaluated the incidence of early (<1 week after injury) and late posttraumatic seizures (>1 week) in 490 consecutive patients admitted to a rehabilitation program for postinjury problems in education and employment [22]. Based on this patient population, the study involved mainly those with moderate-to-severe TBI, although patients with the most severe injuries were excluded as they were unlikely to be admitted to the rehabilitation facility. Early posttraumatic seizures were seen in 16.3% of all patients and were significantly more likely in patients under age 8. PTE was observed in 25.3%, and those with early seizures or depressed skull fractures had a statistically significant increased risk.

The Military Experience

Much of what is known about TBI and the development of PTE stems from studies of combat veterans from World War I to present-day conflicts. With rates as high as 50%, the general risk of PTE in the traumatic-brain-injured military population is substantially higher than in the civilian population. This increased risk has been associated with a higher proportion of severe traumatic brain injuries, particularly those involving dural penetration. Over time and conflicts, the incidence rate of PTE following projectile injuries has remained remarkably consistent. As seen in civilian studies, the rate of development of PTE is highest in the first year, following injury across all injury severities. The incidence of epilepsy within 5 years of injury ranges from 22% to 43% and is approximately 50% by 10 years: evidence that a significant number of veterans develop epilepsy many years after injury [2].

The Vietnam Head Injury Study (VHIS) has provided some of the most extensive longitudinal data regarding the development of PTE after severe TBI. Of the 421 Vietnam veterans with penetrating head injury, 53% had PTE 15 years after injury [9]. Moreover, the risk of developing PTE within one year of injury was nearly 580 times that of the general age-matched population. Ten to fifteen years later, the risk of developing PTE in this population was still 25-times higher than the general population. Phase 3 of the VHIS evaluated 199 of the original VHIS veterans and demonstrated the prevalence of seizures to be 43.7%, 30–35 years after injury, similar to the prevalence found in phase 2, 20 years earlier [23]. In addition, 12.6% experienced very late onset of PTE, with their first seizure occurring more than 14 years after injury.

Naturally, the data from prior wars are cause for serious concern over the injuries and their possible life-long consequences for current military service members who have fought in the wars in Iraq and Afghanistan. TBI has been dubbed the "signature injury" of these conflicts, and combat-related injuries have shifted from penetrating injuries to those related to effects of explosive blast exposure [5]. The majority of injuries in recent wars such as Operation Enduring Freedom (OEF) and Operation Iraqi Freedom (OIF) were blast-related [24]. The incidence of TBI in OIF and OEF is also higher than in past conflicts. In 2005, before policy changes were implemented in late 2006 and 2011 leading to improved TBI documentation, nearly 22% of the wounded service members evacuated to Landstuhl Regional Medical Center in Germany had sustained injuries to the head, face, or neck [25], a percentage that experts believe can serve as a rough estimate of the incidence of TBI in the current conflicts and, in fact, likely significantly underestimates the true percentage [26]. Postdeployment diagnoses of TBI occurred in 9.46 per 100 active duty service members who had been deployed to Afghanistan or Iraq between 2003 and 2014 and those returning from assignments in Korea or Japan, based on a study by the Armed Forces Health Surveillance Center. In this study, the probability of TBI diagnosis after serving in Iraq or Afghanistan was almost double compared to Korea or Japan [27].

In the Vietnam War, only 12–14% of all combat casualties had sustained a head injury [25]. While the mortality rate for service members sustaining head injury in previous wars was quite high – approaching 75% in the Vietnam war – many more of our current service members are surviving their injuries because of faster access to improved medical care and better body armor. As a result, we are likely to see a significant number of soldiers returning from the recent wars with TBI and potentially PTE.

Pugh and coauthors [16] have looked at epilepsy and TBI in Afghanistan and Iraq by reviewing inpatient and outpatient records and ICD-9 codes of veterans of OEF/OIF. They identified 37,718 patients previously diagnosed with TBI, which they divided into categories of penetrating TBI (pTBI) versus other TBI – mild, moderate, severe, and unclassified – as well as 2719 veterans with epilepsy. Those with epilepsy were more likely to have a previous TBI diagnosis and were also more likely to be younger, Caucasian, and have a diagnosis of psychiatric disease. Adjusted odds ratios (AORs) were significant for all levels of TBI and epilepsy, with the lowest AOR being 1.28 for mild TBI (95% CI 1.07-1.53) and the highest AOR among pTBI patients (19.04, 95% CI 9.39-38.84). Thus, data from most recent conflicts support that there is some association between mild TBI and PTE; however, penetrating and severe TBI remain significantly more robust risk factors, as seen in Fig. 4.

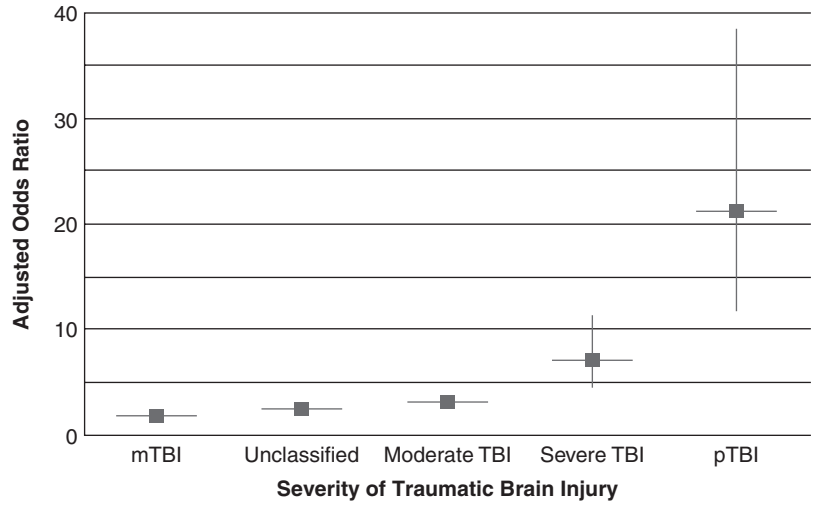


Fig. 4 Association of TBI severity with epilepsy: TBI diagnosed 2009-2010. (Used with permission of Wolters Kluwer from Pugh et al. [16])

Table 1 Published studies comparing rates of early and late seizures after traumatic brain injury

Study	Year	Feature	N (patients with TBI)	Early Seizure %	Late Seizure %
Jennett and Lewin [19]	1960	Admitted	896	4.2	10.2
Annegers et al. [18]	1980	Population	2747	2.1	1.9
Desai et al. [63]	1983	Admitted, pediatric	702	4.1	N/A
Salazar et al. (VHIS) [9]	1985	Military, penetrating head injury	421	N/A	53
Hahn et al. [64]	1988	Admitted, pediatric	937	9.8	N/A
Annegers et al. [11]	1998	Population	4541	2.6	2.1
Angeleri et al. [20]	1999	Admitted	137	8	13.1
Asikainen et al. [22]	1999	TBI rehab center	490	16.3	25.3
Englander et al. [21]	2003	Admitted with CT findings or GCS 3-10	647	3	10.2
Christensen et al. [14]	2009	Population	78,572	N/A	1.3
Raymont et al. (phase 3 of VHIS) [23]	2010	Military, penetrating head injury	199	N/A	43.7
Yeh et al. [17]	2013	Population	19,336	N/A	1.9
Pugh et al. [16]	2014	Military	422	N/A	N/A[a]
Mahler et al. [15]	2015	Population, case–control	422	N/A	N/A[b]

VHIS Vietnam Head Injury Study
[a]Could not assess due to cross-sectional design
[b]Could not assess due to case-control design

Table 1 summarizes adult and pediatric population-based and military studies on rates of seizures post TBI.

TBI and Psychogenic Nonepileptic Seizures

In addition to seizures and epilepsy, TBI is also associated with the development of psychogenic nonepileptic seizures (PNESs), although this has not been extensively studied. PNESs are defined as seizure-like episodes that lack the characteristic ictal EEG manifestations of epileptic seizures. While the etiology of PNES is unclear, these events are thought to represent a reaction to an overwhelming physiologic arousal in people with a history of severe, often repeated stress and/or psychological or physical trauma. There is a high rate of comorbid psychiatric disease among people with PNESs, including posttraumatic stress disorder (PTSD) [28]. PNES is common in the veteran population, comprising 25% of admissions to epilepsy monitoring units (EMUs) at Veterans Affairs medical centers [29], and veterans with PNES have markedly increased rates of PTSD. Among a population of veterans, Salinsky and associates [30] found that recurrent seizures following TBI were more likely to represent PNES than epileptic seizures. In this study, TBI was the proposed etiology of seizures in 57% of Veterans eventually confirmed by video-EEG to have PNES versus 35% of Veterans eventually confirmed to have epilepsy. Mild TBI was the most common type of TBI among PNES patients, occurring in 87% of PNES patients compared to 37% of epilepsy patients. Therefore, it seems that mild TBI conferred a higher risk of PNES than of epilepsy. The authors of this study have postulated that the link between TBI, particularly mild TBI, and PNES could be explained by the mutual association with PTSD; however, this is yet to be confirmed. Another study examining a population of OEF/OIF veterans diagnosed with both epilepsy and TBI (largely from blast injury/mild TBI) found that 44% of this population likely had PNES and that a large percentage (81%) of these veterans met criteria for PTSD [31], which lends support to the hypothesis of Salinsky and associates [30] .

Timing and Types of Seizures

The exact timing of PTE onset varies widely. Most studies indicate that the risk of developing PTE is highest in the first 1–2 years post injury.

Table 2 Relative risk and 95% confidence intervals for unprovoked epileptic seizures by severity and time since TBI

Time after injury by severity of TBI	No. Cases	No. Controls	RR	95% CI
Mild TBI				
0–0.5 years	8	8	8.1	3.1–21.7
0.5–2 years	6	19	2.6	1.0–6.4
2–10 years	19	104	1.5	0.9–2.4
>10 years	33	135	2.0	1.4–2.9
Severe TBI				
0–0.5 years	12	2	48.9	10.9–218.9
0.5–2 years	12	9	10.9	4.6–25.8
2–10 years	14	16	7.1	3.5–14.6
>10 years	3	11	2.2	0.6–8.0

Cases cases with unprovoked seizures, *RR* Relative risk, 95% CI 95% confidence intervals, *TBI* traumatic brain injury. Mild TBI (ICD-8, ICD-9: 850; ICD-10: S060); severe TBI (ICD-8, ICD-9: 851-854, ICD-10: S061-S069) Used with permission of John Wiley and Sons from Mahler et al. [15]

Data from the VHIS revealed that while 57% of PTE developed within one year of injury, over 18% experienced their first seizure more than 5 years after injury, and 7% experienced their first seizure 10 or more years after injury [9]. Others have demonstrated 80% of PTE presents within the first year, with up to 90% by 18 months [21]. The data mentioned earlier from phase 3 of the VHIS demonstrated new cases of PTE even 30–35 years after injury. After mild TBI, the risk of PTE also remains elevated even 10 years after initial injury based on recent large population studies, although risk is still highest in the first six months after injury [14, 15]. Table 2 demonstrates the decrease in relative risk of PTE over time in the large Swedish case-control study from Mahler and associates [15]. Exactly how long the risk remains elevated is unclear, and although it seems certain that the risk of developing PTE many years after injury persists, it becomes difficult to accurately estimate this risk as people develop other independent risk factors for epilepsy as they age (e.g., stroke or dementia).

Seizure types observed in PTE have been examined in a few studies with slightly disparate results. Typically, early seizures immediately following TBI are generalized tonic-clonic [32], while late seizures tend to have focal onset. This may be partially explained by the fact that generalized tonic-clonic seizures may come to the attention of providers earlier; however, studies have consistently shown that a large portion of patients with PTE have focal seizures. Specifically, Haltiner and associates [33] observed 60 patients with moderate-to-severe TBI and found that 31 had generalized seizures, 20 had focal-onset seizures, and 9 had focal-onset seizures with secondary generalization. Similar percentages were noted by Englander and associates [21] in their study of patients admitted to trauma centers. In phase 3 of the VHIS trial, the most common clinical seizure type experienced was focal-onset seizures with alteration of consciousness (formerly called complex partial seizures). A more recent study showed a high rate of localization-related epilepsy among patients with PTE referred to an EMU; in this study, localization-related epilepsy was diagnosed in 93% of PTE patients, arising mostly from temporal or frontal lobes [34]. Seizures in PTE tend to arise preferentially from frontal/temporal regions rather than occipital/parietal areas, likely because TBI most commonly affects the frontal and temporal lobes [35].

Diagnostic Testing

Even today, diagnostic testing to predict the development of PTE is quite limited and often adds little to the clinical evaluation and consideration of the previously discussed risk factors. EEG findings in TBI are usually nonspecific and do not predict development of PTE. In a large EEG study, over 1000 EEGs were reviewed from 722 patients [36]. Many of these patients would have been classified as having suffered a severe TBI, and in fact, the rate of PTE in this population was 43%. These records were compared to a control series of EEGs from all TBI patients at another hospital, many of whom sustained mild TBIs. The investigators found no significant difference in the rate of EEG abnormalities between 510 patients with PTE and 391 without, regardless of the time since injury. In addition, they found that 20% of patients with PTE had at least one normal EEG within the first 3 months post injury. As such, the authors ultimately concluded

that EEG added little to the clinical evaluation when determining likelihood of PTE after TBI.

Brain imaging can demonstrate evidence of prior traumatic injury and can, therefore, be helpful in predicting the development of PTE. CT scans can be obtained readily and easily at most medical centers, but are typically only useful in predicting PTE after severe TBI. Perhaps the earliest study to investigate the ability of CT scans to predict PTE investigated 233 patients admitted for head trauma from 1977 to 1978 [37]. Head injuries were divided into two groups: severe injuries – characterized by loss of consciousness greater than 24 hours, focal neurologic signs, early seizures, depressed skull fracture, intracranial hematoma, or brain contusion – versus mild-to-moderate injuries, which encompassed all other forms of TBI. Eleven patients (5%) developed PTE, all of whom fell into the severe TBI category. In this particular study, only patients with radiographic evidence of a focal cerebral lesion developed PTE, and the risk seemed particularly elevated with the combination of intracerebral hemorrhage coupled with extracerebral hematoma. Data from the VHIS demonstrated a significant relationship between total brain volume loss as measured on CT scan 15 years after injury and the development of PTE [9]. In addition, independent of brain volume loss, location of injury (i.e., resulting in hemiparesis, aphasia, visual field loss, or organic mental disorder) also conferred a higher risk of PTE.

In contrast to its utility for evaluating severe TBI, head CT is typically insensitive to changes from mild TBI and is, therefore, unlikely to be helpful in predicting PTE in this population. A prospective study from India included 381 consecutive patients admitted for mild head injury, GCS 13-15 [38]. Thirty-eight percent were found to have positive findings on CT scan, and these abnormal scans were predicted by low GCS admission score [13–14], abnormal neurologic exam, and fractures detected on skull X-rays. Accordingly, the decision to image a patient should be based on clinical presentation and, at this point in time, imaging is not recommended for most patients with mild TBI to predict risk for PTE.

Magnetic resonance imaging (MRI) has higher resolution and is more sensitive to brain injury; therefore, this may be a more promising diagnostic tool for PTE. Angeleri and colleagues [20] compared MRIs from 137 patients with TBI. In particular, they were interested in the presence of hemosiderin one year after injury. While there was no difference in the percentage of patients with "isolated hemosiderin zones," the group with PTE was significantly more likely to have focal gliotic hemosiderin lesions in their cortex, again underscoring the importance of lesion location. In a study from India in 2003, Kumar and colleagues [39] employed Magnetization Transfer (MT) MRI to predict PTE. MT imaging, a novel MRI sequence, had previously been utilized for more accurate detection of diffuse axonal injury and perilesional gliosis in neurocysticercosis-related seizures [39]. They found that MT abnormalities extending beyond the lesion seen on standard T2 imaging predicted a higher rate of PTE and that, while hemosiderin alone did not confer a higher risk of PTE, gliotic scar surrounding hemosiderin did. Other advanced MRI techniques such as susceptibility weighted imaging and diffusion tensor imaging are being investigated as means to identify TBI and predict PTE, as these imaging modalities can detect microhemorrhages and white matter injury, respectively [40–42].

Treatment

Numerous trials have been undertaken to evaluate the potential for medications to be truly antiepileptogenic and prevent the development of PTE. Most trial designs included a period of monitoring after the medication had been stopped to see if the drug was truly antiepileptogenic or whether it was merely suppressing seizures. However, while most of the trial designs were similar, there was some variability in time to treatment following injury, length of follow-up, and monitoring of compliance [43].

The largest study to date of early antiepileptic drug (AED) treatment after TBI was a randomized, double-blind, placebo-controlled study evaluating the effectiveness of phenytoin in preventing

PTE in 404 patients with severe TBI [44]. Patients were randomized to either phenytoin or placebo, and treatment was initiated within 24 hours. The patients were treated for one year, during which time serum drug levels were monitored to ensure compliance. Treatment was discontinued after one year, and the patients were followed for a second year to assess potential antiepileptogenic effects of early treatment. The investigators found that treatment with phenytoin significantly reduced the number of early seizures (those occurring in the first week after injury); however, it did not lead to a lower chance of experiencing late seizures or PTE. In the phenytoin group, 3.6% had early seizures versus 14.2% assigned to placebo (risk ratio 0.27, CI 0.12-0.62). Between day 8 and the end of the first year of treatment, 21.5% in the phenytoin group and 15.7% in the placebo group experienced late seizures. By the end of the second year, the rates were 27.5% and 21.1% in the phenytoin and placebo arms, respectively. A small, similarly designed study also found no difference in the rate of PTE in children given phenytoin versus placebo [45].

Multiple other studies have investigated the potential antiepileptogenic effects of some of the older anticonvulsants for either monotherapy or combination therapy. Data from studies of phenobarbital monotherapy and phenytoin combined with phenobarbital were inconclusive because of small sample sizes resulting in wide confidence intervals [43]. One study of carbamazepine monotherapy demonstrated a significant reduction in early seizures but no effect on late seizures [43]. A single study compared valproate to phenytoin for the treatment of early seizures and the prevention of late seizures [46]. There was no significant difference in the rate of early seizures between the valproate and phenytoin treatment groups, and valproate had no significant effect on the rate of late seizures. These treatment trials are well summarized in Fig. 5 adapted from Temkin *Epilepsia* 2009 [43].

In 2003, the American Academy of Neurology released a practice parameter discussing the use of antiepileptics for prophylaxis in severe TBI [47]. They concluded that phenytoin prophylaxis was effective in decreasing the risk of early

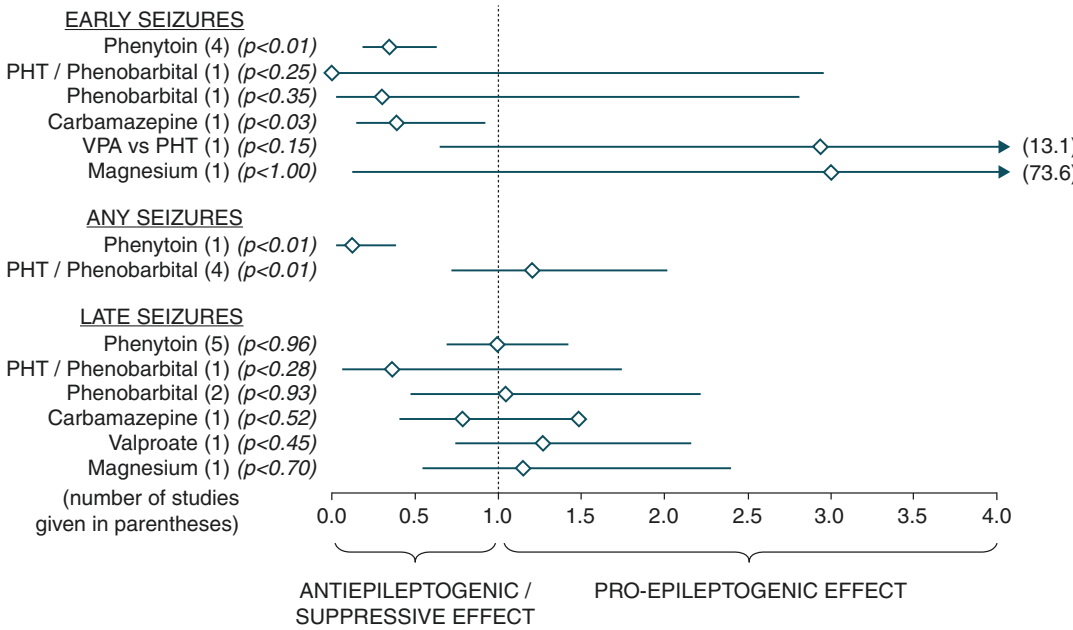


Fig. 5 Meta-analysis results for seizure prevention after traumatic brain injury. The relative risk for each drug and time frame is marked by a diamond on a line that indicates the 95% confidence interval for that relative risk. A relative risk of 1, representing no treatment effect, is marked by the dashed vertical line. (Used with permission of John Wiley and Sons from Temkin et al. [43])

(within one week of injury) posttraumatic seizures, and it was stated that antiepileptic prophylaxis was likely not effective in decreasing the risk of late posttraumatic seizures. In addition to phenytoin, levetiracetam has recently gained popularity for post-TBI prophylaxis, since it is associated with fewer adverse effects and monitoring considerations. Szaflarski and colleagues [48] performed a prospective, randomized, single-blinded comparative trial of levetiracetam versus phenytoin in patients with TBI or subarachnoid hemorrhage, in which levetiracetam was shown to have efficacy comparable to phenytoin in preventing early seizures after TBI and also was associated with improved disability scores at 3 and 6 months and fewer side effects compared to phenytoin. However, at this time, there have been no randomized, double-blind controlled trials comparing levetiracetam and phenytoin after TBI.

Initiation of a chronic AED is warranted after the first late seizure experienced by a patient with TBI due to the high risk of recurrent seizures [33]. Choice of AED in PTE should mirror general practice for other patients with epilepsy and is often guided by the individual patient's comorbidities and by practical considerations such as titration rate, dosing schedule, cost, and potential drug–drug interactions.

Often seizures in PTE cannot be completely controlled with medication alone, especially since structural brain abnormalities increase the likelihood of developing medically refractory epilepsy [49]. In these cases, surgical therapy may be an option and should be considered for patients with PTE, although little has been reported on the subject. TBIs rarely result in the development of mesial temporal sclerosis, but lesionectomies or resective surgeries of an identified epileptic focus are possible.

In addition, a vagal nerve stimulator may be considered in patients with frequent seizures. One case-control study found that VNS was associated with greater reduction in seizure frequency in patients with PTE than in patients with non-PTE at two years of follow-up, with 78% of PTE patients experiencing a greater than 50% reduction in seizure frequency versus 61% of non-PTE patients after 24 months [50]. Responsive neurostimulation (RNS) is a direct form of neuromodulation, which, unlike VNS, functions in a closed-loop manner, detecting initial seizure activity and then "counterstimulating" to abort the seizure. RNS has recently been shown to decrease seizure frequency in patients with medically refractory epilepsy [51] and may be beneficial for patients with PTE and multifocal seizure onset or seizure foci not amenable to surgical resection. A related technology is deep brain (anterior thalamic nucleus) stimulation, which may soon be approved for use in the United States [52, 53].

Figure 6 shows a suggested treatment algorithm for PTE as outlined in Rao and Parko's recent review of PTE [54]. Due to the expanding

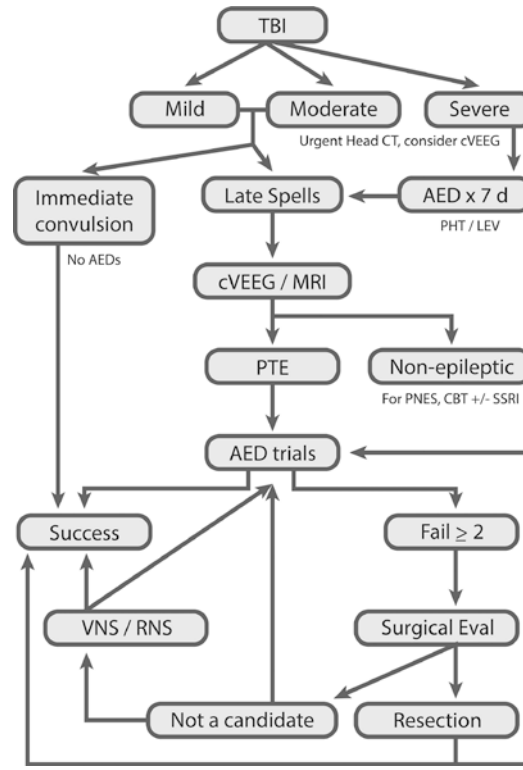


Fig. 6 An algorithm for the management of posttraumatic epilepsy. (*AED* antiepileptic drug, *CBT* cognitive–behavioral therapy, *CT* computed tomography, *cVEEG* continuous video-electroencephalography, *LEV* levetiracetam, *MRI* magnetic resonance imaging, *PHT* phenytoin, *PNES* psychogenic nonepileptic seizure, *PTE* posttraumatic epilepsy, *RNS* responsive neurostimulation, *SSRI* selective serotonin reuptake inhibitors, *TBI* traumatic brain injury, *VNS* vagus nerve stimulation. (Used with permission of George Thieme Verlag from Rao et al. [54]))

nonpharmacologic treatment options for epilepsy therapy, referral to a comprehensive epilepsy center is warranted for patients with PTE, especially in medically refractory cases.

Outcomes

Spontaneous remission rates for PTE range from 25% to 40%: a large number of patients will remain on antiepileptic medications for their lifetime [55]. It stands to reason that people with frequent seizures during the first year after injury will continue to have frequent seizures and have a smaller chance of remission. Thus, outcomes are affected not only by the injury and PTE but also by the treatments used to suppress seizures, and both medical and surgical therapies may have significant side effects.

A study of World War II veterans with penetrating head injuries demonstrated that mortality rate of veterans with head injury coupled with PTE was 1.5 times higher than those with head injury alone [56]. Others found that the presence of PTE correlated with a lower level of overall general function as measured by the Glasgow Outcome Scale in mainly moderate and severe TBI rehabilitation patients [22]. In the same study, the authors found no difference in the rate of independent employment between TBI patients with and without PTE, with approximately one-third being unable to work in each group.

Pathophysiology

As mentioned previously, early posttraumatic seizures do not constitute PTE and are felt to be an epiphenomenon of the underlying brain injury or a marker for the severity of injury [13]. Accordingly, early and late seizures should be considered separately and are believed to have different pathologic mechanisms. This concept is further supported by the ability to suppress early seizures with antiepileptic medications without significantly altering the incidence of PTE. The exact pathophysiologic mechanisms underlying PTE are not completely understood and continue to be investigated. Evidence suggests a multifactorial process including contributions from blood–brain barrier changes, parenchymal hemorrhage, release of excitotoxins, and free radical damage [13]. More specifically, the pathophysiology varies according to the type of injury. Closed head injuries cause edema, diffuse axonal injury, and ischemia, resulting in the release of toxic mediators [7]. Penetrating injuries lead to the formation of epileptogenic focal cortical scars. Evidence also exists linking hemorrhagic infarction to the formation of an epileptic focus through ferrous deposits and a resulting cascade that culminates in cell death [7]. Development of late seizures is likely due to alteration in inhibitory and excitatory circuits of the hippocampus and cortex, leading to overexcitation. Rat models have demonstrated reduction in GABA signaling of dentate gyrus, and molecular analysis of the hippocampi of PTE patients demonstrates focal cell loss in the dentate gyrus and mossy fiber sprouting occurring days to weeks after TBI. This finding has led to exploration into medications such as imipramine, a tricyclic antidepressant, to stimulate hippocampal neurogenesis in rat models of TBI [57]. Recent data indicate that genetic variability may account for differences in an individual's risk for seizures after TBI. Specifically, a polymorphism in a gene encoding interleukin-1 beta (IL-1β), which is involved in the inflammatory response after head injury, has been associated with an increased risk for developing PTE [58].

Epileptogenesis

Epileptogenesis involves the process whereby the normal, nonepileptic brain transforms into one that generates spontaneous, recurrent, and unprovoked seizures [59]. TBI provides one of the clearest models of epileptogenesis in that an inciting injury results in the development of posttraumatic seizures. One key feature of this process that has been identified through observation, as well as through animal models, is the presence of a latent period between the injury and the onset

of seizures. As previously discussed, this latent period is quite variable and can last for years in humans. Researchers have focused on this period of time to identify the various changes that occur in the brain during epileptogenesis and view it as a critical time period to target truly antiepileptogenic therapies.

The cascade of changes that occur following a TBI is quite complex. Some early changes involve gene induction and neurotransmitter modifications as well as modifications of ion channel and transporter proteins [59]. Within a few days after injury, there is evidence of neuronal death and inflammation. The later changes include axonal sprouting and dendritic modifications, such as mossy fiber sprouting – in essence the formation of abnormal excitatory connections [60]. Some models of epileptogenesis have demonstrated structural alterations in interneurons leading to less effective GABAergic inhibitory neurotransmission [60].

In an effort to better understand the various processes that define epileptogenesis, researchers have attempted to create animal models of TBI and PTE. Naturally, this is fraught with difficulties as brain injury is a very heterogeneous disorder that differs from person to person in terms of the location of injury, mechanism of injury, and extent of injury. The two main animal models for PTE are the rat lateral fluid-percussion model, which has been reported to consistently result in late spontaneous seizures [61], and the controlled cortical impact model. The rat lateral fluid-percussion model involves craniectomy followed by direct impact to the epidural space using a liquid pressure pulse transmitted via a saline-filled cylinder [61]. The severity of injury can be controlled by the weight and height of a pendulum that strikes the cylinder creating the liquid pulse. This mode of injury mimics human TBI well in that it causes direct cortical injury as well as deep white matter damage. From this model, researchers have begun to study diagnostic and predictive technologies, including imaging and electrophysiologic techniques. In addition, they have begun to study novel therapies such as medications that block glutamate receptors or calcium channels, caspase inhibitors, antiapoptotic agents, and stem cell transplantation yet [59]. Recently, the controlled cortical impact rat model has also been shown to cause PTE, that is, seizures occurring greater than a week from head injury. This method uses a pneumatic impactor to damage intact brain and has the advantage of causing a more precise and reproducible injury, simulating various degrees of TBI severity [62]. Despite some successes, none of these treatment strategies have been translated to human trials [59].

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Posttraumatic Hypopituitarism: Neuroendocrine Dysfunction and Treatment

Dennis J. Zgaljardic, Lisa Kreber, Jack Foreman, and Randall Urban

Introduction

Traumatic brain injury (TBI) contributes to a substantial number of deaths and cases of permanent disability in the United States annually. Life-long consequences of sustaining a TBI can include impairments in physical, cognitive, and psychosocial functioning [1]. The Center for Disease Control (CDC) estimates that at least 5.3 million Americans, ~2% of the United States population, are dependent on the care of another person to perform activities of daily living as a result of TBI [2]. Brain injury severity (typically assessed by alternation of or duration of loss of consciousness [LOC] and posttraumatic amnesia [PTA], as well as Glasgow Coma Scale [GCS]) is associated with the development of cognitive deficits and personality/behavioral changes in the acute period [3]. Moderate-to-severe TBI can result in significant loss of function in the areas of motor skills, communication skills, sensation, emotional stability, psychosocial adjustment, and a range of cognitive parameters that can render an individual unable to function in society at premorbid levels of functioning in the postacute period [4]. LOC is not considered a reliable predictor of future outcomes post-TBI and is measured as follows: <30 minutes = mild; 30 minutes–24 hours = moderate; >24 hours = severe. PTA (i.e., <1 day = mild; 1–7 days = moderate; >7 days = severe) is the period of time from injury onset to the return of continuous day-to-day memories, and is typically viewed as a more robust predictor of length of hospitalization, recovery rates, and functional outcome [5, 6]. Patients experiencing PTA can display heightened levels of aggression and agitation including disorientation, impulsive behaviors, irritability, confabulatory responding, amnesia (retrograde and anterograde), and impaired attentional skills that may be initiated or prolonged by overstimulating environmental factors [7]. Another measure of TBI severity is the 15-point GCS, which includes an assessment of the patient's level of consciousness, orientation, and motor initiation. GCS scores of 13–15, 9–12, and 3–8 indicate mild, moderate, and severe levels of TBI, respectively [3]. The GCS score is typically viewed as a rough estimate of TBI severity, because the designation of coma can be influenced by many factors [8].

Pituitary dysfunction following TBI was initially reported early in the twentieth century [9];

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however, the possibility that acute TBI can result in pituitary dysfunction has only recently been appreciated [10–12]. Approximately two-thirds of individuals who have come to autopsy following TBI have been found to have structural abnormalities of the pituitary, pituitary stalk, and/or hypothalamus [13]. Hence, the hormones produced by the pituitary gland or regulated by the pituitary axis may be negatively impacted by TBI. Chronic dysfunction of the pituitary axis is observed in approximately 35% of individuals who sustain a moderate-to-severe TBI. The most common deficiency is that of growth hormone (GH), followed by gonadotropin, cortisol, and thyroid hormones (T3 and T4) [14]. Previous work has demonstrated that hypopituitarism, particularly growth hormone deficiency (GHD), is common among survivors of TBI [15]. The prevalence of GHD in patients with TBI varies within the range 10–25% [11]. GHD is associated with multiple physical, metabolic, and neuropsychological manifestations, including, but not limited to, diminished lean body mass, disrupted lipoprotein and carbohydrate metabolism, reduced bone mineral density, and impaired cardiac function, as well as declines in cognitive functioning, fatigue, and diminished quality of life (QoL) [16, 17]. Therefore, providing appropriate diagnosis of GHD in patients with the aforementioned symptoms is crucial, as subsequent management using GH replacement therapy has been shown to improve cognitive, psychiatric, and physical symptoms [17–21].

The purpose of this chapter is to provide an update of the literature with regard to posttraumatic hypopituitarism (PTH) and to relate these findings to neuroendocrine dysfunction and symptom detection and management. While PTH can result in multiple neuroendocrine abnormalities, it has become clear that GHD is most common. Findings from recent studies indicate that, in a significant proportion of patients with moderate-to-severe TBI, observed cognitive, psychiatric, and physical/functioning sequelae may be attributed, in part, to GHD with a good potential for symptom improvement following GH replacement. It is our view that moderate-to-severe TBI is a chronic disease process and the physical/functioning, cognitive, and psychiatric consequences of untreated endocrinopathies are extensive and detrimental to functional outcomes.

Posttraumatic Hypopituitarism (PTH)

The adult pituitary gland is a pea-sized structure (approximately 600 mg in weight) and lies beneath the brain in the middle cranial fossa. The pituitary gland sits within a bony cave called the sella turcica and is connected to the hypothalamus by the pituitary stalk. The superior hypophyseal arteries branch from the internal carotid artery to supply the hypothalamus. The long and short hypophyseal vessels (which form the hypothalamic portal circulation) provide the blood supply to the pituitary gland. Severed portal vessels are capable of regeneration and, therefore, permit some resumption of anterior pituitary function post injury, although this process is likely to be quite slow and not always complete [22]. Following trauma to the head, the vascular supply to the pituitary gland is tenuous, but confinement of the pituitary within the sella turcica by the diaphragma sella renders the infundibulum and stalk vulnerable to shearing. As cortical swelling is limited by the skull following brain injury, pituitary gland is also swelling, limited by its bony encasement. Pituitary gland compression will include that of the long portal vessels between the stalk and the free edge of the diaphragma sella. The fragile vessels are also susceptible to pituitary stalk rupture or transection as well as vasospasm and hypotension [8].

The structurally larger part of the pituitary, the anterior lobe, is more glandular than neuronal in appearance. Neural cells within the hypothalamus synthesize specific inhibiting and releasing hormones, which are secreted directly into the portal vessels within the pituitary stalk. The portal vessels then carry these hormones to the secretory cells within the anterior lobe. The somatotrophs, responsible for the secretion of GH, constitute approximately 40% of pituitary cells. The corticotrophs,

responsible for adrenocorticotropic hormone (ACTH), constitute approximately 20% of the anterior pituitary cells. The thyrotrophs, which secrete thyroid stimulating hormone (TSH), constitute 5% of the anterior pituitary cells, and are located in the anterior medial region of the gland. The gonadotrophs secrete follicle-stimulating hormone (FSH) and leutinizing hormone (LH) and constitute 10–15% of the anterior pituitary cells [23]. Prior work has suggested that the most common hormonal dysfunction following PTH is GHD resulting from somatotrophic cell death due to impaired blood and oxygen supply [12, 24]. The least common pituitary abnormality noted post TBI is TSH deficiency [25].

The most probable mechanisms of PTH are (1) primary physical effects of brain damage, (2) indirect injuries, such as hypoxia or hypotension, and/or (3) the transient effects of critical illness and medication. Direct mechanisms refer to fractures through the skull base and sella turcica, as well as the shearing injuries of the pituitary, infundibulum, and/or hypothalamus. Transection or rupture of the pituitary stalk results in anterior pituitary lobe infarction because of disruption of the portal blood supply from the hypothalamus to this region. Indirectly, functional damage at the hypothalamic–pituitary region can be the result of a secondary hypoxic insult. Another possible means of damage is diffuse axonal injury (DAI) caused by acceleration–deceleration along with rotational forces, common in motor vehicle crashes [14].

PTH has been associated with adverse effects in patients in the acute or chronic stages, including reduced QoL and rehabilitation outcomes with direct adverse effects on health outcomes including ischemic heart disease and increased mortality [8, 26–32]. It is important to mention that hypopituitarism can present without TBI. The incidence of idiopathic clinically apparent hypothyroidism is approximately 2% in adults and is 10-times more common in females than males [33]. The incidence, however, of subclinical or asymptomatic GHD, hypogonadism, or hypocortisolism is unknown. Although it is certainly possible that an individual with PTH may have had pre-existing asymptomatic hypopituitarism (especially hypothyroidism), the numbers most likely would be very small, as deficiencies in these other axes would be clinically apparent.

Neuroendocrine Dysfunction: Prevalence, Symptom Detection, and Hormone Screening

Determining a "true" prevalence for neuroendocrine dysfunction following TBI has been difficult due to methodological differences between studies, including timing of hormone assessments post-TBI, injury severity, age of onset, types of hormones studied, and the methods used to diagnose pituitary hormone dysfunction. Hence, these factors need to be taken into account when comparing across studies. Prevalence of anterior hypopituitarism in the chronic phase of TBI varies, ranging from 15% to 50% with GHD prevalence ranging from 6% to 33% in the chronic phase of recovery [11, 12, 34–43].

Aimaretti and associates examined pituitary hormone levels in patients with mild, moderate, and severe levels of TBI at 3 months and 12 months post injury [35]. PTH was found in 33% of patients at 3 months and 23% of patients at 1 year. Seventy-five percent of the patients with single or multiple axis abnormalities at 3 months had reverted to normal at 12 months. Conversely, 6% of patients who had normal pituitary hormone levels at baseline developed single-axis PTH at 1 year, and 13% who had single-axis deficiencies at 3 months had developed multiple deficiencies at 1 year. Interestingly, of the 32 patients with a GCS score of 13 or greater at time of injury (i.e., mild), 13 (41%) had chronic pituitary deficiencies, suggesting that the incidence of PTH in mild TBI (mTBI) is considerable. Similarly, Benvenga and associates reported a case series of more than 300 patients with pituitary dysfunction secondary to TBI [10]. Hormonal abnormality was common in their sample, with indications that such abnormalities can readily occur in those individuals with mTBI. Krahulik and associates followed 89 patients with PTH over time and discovered that 21% had developed hormonal dysfunction [44].

Deficits in the somatotropin axis were most common, followed by hypogonadism. As with the Aimaretti and coauthors study noted above, Krahulik and coauthors also observed patients who recovered their normal axis function over time and also found patients who were normal at the time of injury or at 3 months postinjury who subsequently developed PTH [44]. Schneider and coauthors reviewed the prevalence of PTH in 825 patients at least 5 months post injury in a multicenter study performed in Austria and Germany [45]. They discovered at least one hormonal abnormality in 38% of patients. The prevalence of PTH in individuals with mild, moderate, and severe TBI was 17%, 11%, and 35%, respectively, again demonstrating that individuals with less severe injuries are still at risk for developing hormonal deficiencies. In a similar vein, repetitive head trauma from sport-related injuries has become an area of great interest, especially over the past decade. There have been small studies showing a relationship of repetitive head trauma and PTH, including a case report of an adolescent with at least four sport-related concussions who complained of fatigue and was found to have multiple pituitary deficiencies [46, 47]. Further, Kelly and coauthors discovered PTH in 24% of 68 retired profootball athletes [48]. These studies clearly suggest that early pituitary deficits may recover over time, and that, conversely, normal pituitary function early after injury may become abnormal at 3–12 months. Recovery does not appear to occur in those patients who develop deficiencies of all pituitary hormones (i.e., panhypopituitarism).

As described above, hypopituitarism can be one of the immediate consequences of TBI, with some hormone deficiencies resolving over time, while others emerge. However, approximately 6 months post TBI, hormone deficits appear to be stable and relatively permanent [49]. Due to the fluctuations in hormone levels following TBI, consensus guidelines from the American Association of Clinical Endocrinologists and American College of Endocrinologists have recommended that all patients with moderate-to-severe TBI be assessed for neuroendocrine dysfunction during the acute and chronic phases of their recovery and patients with mTBI who are experiencing symptoms should be offered hormone assessment [24, 50–52]. An algorithm for the timing of a baseline hormone workup has been proposed by Ghigo and coauthors and is as follows: For all TBI patients, regardless of severity, hormone assessments should be conducted during hospitalization and if hyponatremia and hypotension are present [24]. Assessments should be repeated at 3 and 12 months after any severity of TBI. Retrospectively, if patients with TBI have any signs or symptoms of hormone dysfunction and are at least 12 months post-TBI, immediate hormone testing should be conducted, as it is unlikely that any hormone deficiencies are transient at this point [24].

Patients with moderate-to-severe TBI typically have deficits that require medical evaluation and/or intervention, which would allow patients with this level of injury severity an opportunity to have symptoms examined and potentially be evaluated for neuroendocrine dysfunction. However, patients with mTBI typically do not present to an emergency room or physician until many months post-TBI. At this point, the symptoms of TBI are often labeled as "postconcussion syndrome" and alternative explanations for persisting symptoms may not be readily explored. As discussed above, neuroendocrine dysfunction can occur with all severity levels of TBI; however, it has been primarily investigated in patients with moderate-to-severe TBI. Schneider and coworkers published a systematic review of hypopituitarism following TBI in which they attempted to determine the prevalence of hypopituitarism by injury severity [32]. Studies were reviewed that included all TBI severities [35, 36, 42, 43], only moderate-to-severe TBI [34, 41], and only severe TBI [37, 40]. Results from these studies were inconsistent, as some reported no relationship between hypopituitarism and severity of TBI [34, 35, 37, 41–43], while others reported more frequent rates of hypopituitarism in patients with more severe TBI [36, 38]. All studies that had included all severities of TBI in the chronic phase of recovery were further analyzed, and results from the pooled prevalence of hypopituitarism revealed that the frequency of hypopituitarism was greater in severe TBI (35.3%; 95% CI = 27.3–44.2%) than in moderate

(10.9%; 95% CI = 5.1–21.8%) and mTBI (16.8%; 95% CI = 10.9–25.0%). Future studies are needed to investigate prevalence of specific hormone deficiencies by injury severity.

Despite clear evidence that a large number of survivors of TBI can experience hypopituitarism, few patients are routinely screened as part of their routine clinical workup for TBI. This could be due, in part, to the considerable overlap of symptoms between TBI and hypopituitarism. Symptoms such as memory and concentration impairments, decreased intelligence quotient (IQ), decreased QoL, fatigue, anxiety, depression, social isolation, deterioration in sex life, and increased unemployment, which are frequently reported in patients with TBI, have also been reported in patients with adult-onset GHD and no documented brain injury [11, 24]. These symptoms also tend to be nonspecific to hypopituitarism and could be attributed to many different disorders, including depression, chronic fatigue syndrome, and postconcussion syndrome.

Proper screening and evaluation of pituitary hormones following TBI is essential to definitively diagnose hypopituitarism and potentially treat the underlying cause of these symptoms. Routine basal hormone screening involves assessing each individual axis of the pituitary separately. Serum levels of TSH and free T4 (thyroxine) should be measured to evaluate the thyroid axis. A diagnosis of central hypothyroidism can be made with a normal or low TSH and low levels of free T4 [53, 54]. The gonadal axis is assessed by measuring baseline levels of FSH and LH, along with free and total testosterone levels in men and an estradiol level in premenopausal women who are not menstruating regularly. Central hypogonadism can be diagnosed with low levels of testosterone or estrogens with either normal or low FSH and LH levels [30, 37, 41]. Prolactin levels should also be measured in both sexes as increased levels can indicate underlying structural pathology of the pituitary [53, 55]. Basal hormone levels for the thyroid, gonadal, and prolactin axes are sufficient for a diagnosis [35, 37, 47]. However, adrenal insufficiency and GHD require provocative testing in addition to basal hormone screenings. Adrenal insufficiency can be initially screened by a basal morning cortisol level. If cortisol levels are less than 500 nmol/L, a referral to an endocrinologist is warranted for further assessment, including a dynamic stimulation test to assess adrenal reserve [11].

Insulin-like growth factor-1 (IGF-1) is often used as a surrogate marker of GH levels and is included as part of basal hormone screenings [21, 24, 51]. Reliance on IGF-1 as an assessment of GH function after TBI is standard practice, but its use needs to be re-evaluated, because 50% of adults with GHD have IGF-1 levels within the normal reference range [56]. Similarly, patients with a normal GH response can have low IGF-1 levels [24, 39]. Direct serum assessment is unreliable because of the pulsatile release of GH and results in serum fluctuations within a 24-hour period [57]. Thus, provocative testing is essential to definitively diagnose GHD [24, 51]. Peak GH secretion during provocative testing is used to assess the capacity of the pituitary to release GH [21]. The insulin tolerance test (ITT) is considered the "gold standard" in provocative tests for diagnosing GHD [24, 58, 59]; however, it cannot be safely performed in patients with seizures or severe cardiovascular disease [60, 61]. This contraindication limits its use in patients with TBI. The glucagon stimulation test (GST) has comparable diagnostic accuracy and reliability as the ITT [62] and is well tolerated in patients with TBI [51, 63]. A single provocative test is sufficient for the diagnosis of GHD in adults [64]. It should be noted that basal hormone assessments and the results of provocative tests need to be interpreted within the context of the patient's medical history, clinical exam, and symptoms.

Cognitive, Psychiatric, and Physical/Functioning Sequelae

Cognitive Dysfunction

Regions of the brain that are particularly vulnerable to TBI include the frontal lobe, anterior temporal lobe, corpus callosum, brainstem, and limbic structures, such as the basal ganglia and hypothalamus [65]. Consequently, cognitive and behavioral processes commonly disrupted by

TBI include arousal, attention, speed of information processing, new learning, memory retrieval, fluency, and executive functions (including organization and planning, sequencing, multitasking, judgment, and abstraction) [66, 67]. While the specific neuropsychological impact of PTH remains unclear, GHD due to PTH is associated with changes in body composition, as well as impaired QoL, cognitive disturbance, and psychological sequelae [68]. It is important to mention that the impact of hypopituitarism, particularly GHD, on cognition from causes other than TBI has been studied in children and adults. Both have been associated with cognitive impairments in memory, attention/concentration, and information processing speed [69–75].

Wamstad and coworkers did not report significant group differences on tasks of cognition in children and adolescents with (n = 9) or without (n = 18) GHD (based on provocative testing) following moderate-to-severe TBI [76]. Kelly and coworkers failed to find significant differences in patients who were GHD post TBI on tasks that assess memory and attention/concentration compared to those who were GH-sufficient post TBI [77]. However, compared to patients with normal pituitary function, those with deficits in the GH axis had higher rates of at least one marker of depression, as well as reduced QoL in the domains of physical health, general health, emotional health, pain, energy, and fatigue. Popovic and coworkers assessed the relationship between GHD and cognitive disabilities and mental distress in 67 patients with moderate-to-severe TBI [41]. They discovered a significant relationship with peak GH levels to short- and long-term memory deficits, paranoid ideation, and somatization, as well as an association between lower IGF-1 levels and impaired visual memory. In their study, Leon-Carrion and coworkers were able to demonstrate cognitive impairment in patients with TBI and GHD on neuropsychological tasks that assess attention, executive functioning, and memory compared to patients with TBI who were GH-sufficient [78]. The GHD group demonstrated greater deficits in simple attention, memory (increased errors in intrusion and repetition), increased reaction time, and greater emotional disruption. The results were interpreted as supporting the concept that some deficits post TBI may be the direct result of GHD, rather than being attributable more generally to the brain injury per se.

The mechanism underlying the effects of GH on cognition is not entirely understood. GH receptors are located throughout the brain. From the animal literature, it is clear that GH and IGF-1 play a role in modulating the N-methyl-D-aspartate (NMDA) receptor. GH influences the NMDA receptor system in the hippocampus, an essential component of long-term potentiation (LTP), which is highly involved in memory acquisition [79, 80]. Furthermore, there may be a relationship between the NMDA receptor subunit mRNA (messenger ribonucleic acid) expression levels and learning ability. Learning is improved by GH replacement in rats that have had their pituitaries removed [79]. Additionally, following central nervous system injury in humans, IGF-1 has also been found to increase progenitor cell proliferation and numbers of new neurons, oligodendrocytes, and blood vessels in the dentate gyrus of the hippocampus [81]. In contrast, deficiency in GH and IGF-1 decreases survival of dentate granule neurons within the hippocampus [82]. Devesa and associates posited that treatment with GH in patients with PTH may increase the number of newly formed neurons in the hippocampal dentate gyrus, a zone related to recent memory [83].

Psychiatric Symptomatology

Psychiatric symptoms and maladaptive behaviors (e.g., depression and/or behavioral disinhibition) experienced by patients with TBI can be a significant limiting factor for rehabilitation participation and positive functional outcomes [5, 31, 84, 85]. Depression is common following TBI, with prevalence rates estimated to be 30–38% [86]. Given the lifetime prevalence of depression in the United States, which has been reported to be 16.2%, there appears to be an increased risk of developing depression after TBI over and above one's lifetime risk [87]. However, in a cross-sequential analysis, Ashman

and associates found that rates of depression following TBI can decline with time since injury [88]. Many factors coincide with TBI, including pain, fatigue, sleep disturbance, cognitive dysfunction, apathy, decreased mobility, and emotional processing deficits, that can result in the experience of depression by themselves or may have a cumulative effect with a resulting increase in depression risk post TBI [89]. Depression in individuals with TBI can also be the result of a reaction to the injury itself and/or result from other psychological changes; however, emotional and behavioral sequelae can also be the direct result of specific neurotransmitter and/or neuroendocrine system dysfunction [90, 91].

The monoamine deficiency hypothesis purporting that decreased levels of serotonin, norepinephrine, and γ-aminobutyric acid (GABA) result in depression is one theory applied to the experience of depression post TBI [92]. Disruptions of serotonin, glutamate, and dopamine levels have been identified in TBI patients [91]. Another theory is that of dysregulation of the hypothalamic–pituitary–adrenal axis (HPA axis) by physical or emotional stress. Both overactivation and underactivation of the HPA axis have been reported in TBI [55]. This theory posits that the amygdala and hippocampus, structures that regulate emotions and memory, have connections to the hypothalamus and are ultimately affected by neuroendocrine imbalance post injury [93]. Stress-induced cortisol released by the adrenal cortex appears to play a role in depression and is characterized by a more chronic course of depression, hippocampal atrophy, and reduced levels of brain-derived neurotrophic factor [94].

Fatigue and Physical/Functioning Impairment

Fatigue, not to be confused with depression, is typically viewed as a subjective phenomenon that can be expressed, for example, as experiencing a lack of energy or motivation, weakness, and/or sleepiness and has been reported to greatly impact patients' lifestyles by limiting participation in therapeutic, social, and/or leisure activities [95–97]. The association between depressed mood and fatigue post TBI is not entirely clear. The consensus from prior work indicates a consistent, but not necessarily causative, association between subjective fatigue and psychiatric disorder (e.g., depression) in this patient population [98, 99]. In their study assessing potential correlates of fatigue in patients with TBI, Ponsford and coworkers discovered that patients with symptoms related to depression were more likely to report significant levels of fatigue; however, so were patients who also experienced heightened levels of pain and cognitive dysfunction [100]. Zgaljardic and associates have proposed a mechanism of TBI-related fatigue (Fig. 1) [99]. They posited that, as TBI can result in neuropsychological impairment, pain, sleep disorders, and, in some individuals, endocrine dysfunction, the injury can elicit inflammation and oxidative stress initially at injury foci and, later, possibly in additional tissues through indirect effects, such as TBI-induced physical inactivity or mitochondrial impairment secondary to hormone deficiencies, including GH. Mitochondrial and cardiovascular dysfunction, as well as oxidative stress, may contribute to peripheral fatigue (i.e., impaired muscle performance secondary to exertion). Notably, central fatigue-induced (i.e., from a neuropsychological standpoint, a subjective view of one's fatigue symptoms) reductions in physical activity may initiate a self-reinforcing cycle of both central fatigue and peripheral fatigue.

While several factors appear to contribute to symptoms related to fatigue post TBI, GHD warrants specific consideration, as GHD in the absence of TBI is associated with fatigue [101–104]. Thomas and associates reported reduced aerobic capacity in patients with GHD but without TBI that are similar in magnitude to those observed in patients with TBI and GHD [105]. GHD has also been reported in a subset of patients with fibromyalgia, a group in which fatigue is a cardinal characteristic [106–110]. GHD may have a direct impact on skeletal muscle mitochondrial function, as GH stimulates

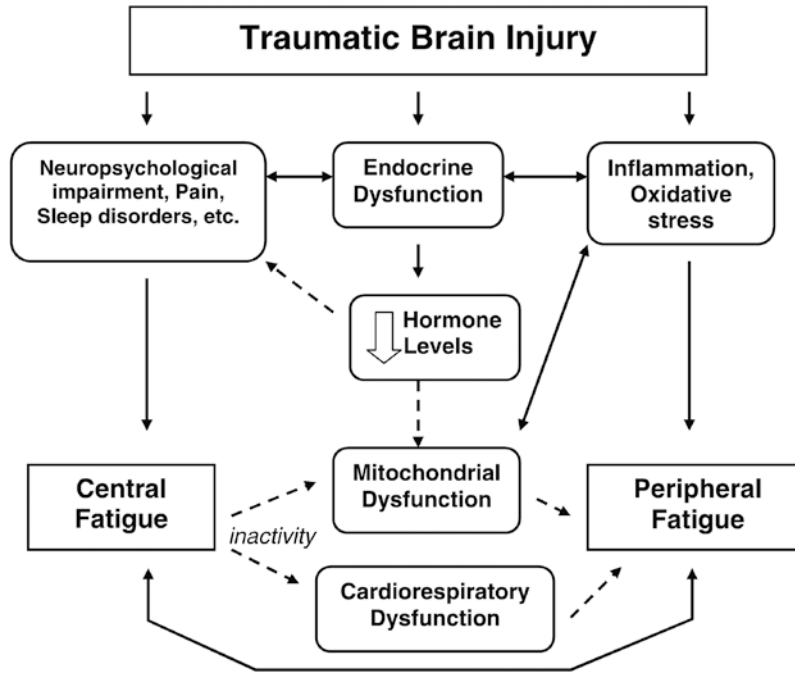

Fig. 1 Proposed mechanism of TBI-related central and peripheral fatigue. (Used with permission of Taylor & Francis from Zgaljardic et al. [99])

skeletal muscle mitochondrial enzyme activity and adenosine triphosphate (ATP) synthesis [111, 112]. Impaired skeletal muscle mitochondrial function may, thus, be partially responsible for the reduced maximal aerobic capacity in individuals with GHD but without TBI [104]. In patients with both TBI and GHD, VO_{2max} (maximum rate of oxygen consumption) is considerably worse relative to patients with TBI and adequate GH levels, which could reflect further impairment of skeletal muscle mitochondrial function [113]. These findings suggest that GH replacement may improve cardiorespiratory capacity in TBI patients with GHD (peak GH level less than 3 ng/mL) and GH insufficiency (peak GH response between 3 and 10 ng/mL).

PTH has been associated with significant negative consequences in physical/functioning. Clinical symptoms associated with hypopituitarism are dependent on the specific hormone axis affected, severity of the hormone deficiency, gender, and whether the deficiency is acute or chronic. Physical symptoms may be nonspecific, such as fatigue, changes in weight, and hypotension, and, as such, are often attributed to the brain injury and not linked to a hormone deficiency. The effects of hormone deficiency may potentially impede progress in rehabilitation, impair recovery, and may even contribute to significant morbidity following TBI [19, 34, 114, 115]. Hormone deficiencies can negatively influence recovery from brain injury, even if the patient is undergoing intense rehabilitation [116, 117]. Understanding the signs and symptoms of hormone deficiency may assist in the timely diagnosis and treatment of hypopituitarism following TBI.

Clinical manifestations of glucocorticoid deficiency can include fatigue, pallor, myopathy, anorexia/weight loss, weakness, hypotension, nausea, and hypoglycemia [32]. These symptoms can be life-threatening and require hydrocortisone therapy as soon as the diagnosis can be confirmed by an ACTH stimulation test [8]. Some of the symptoms of a glucocorticoid deficiency overlap with those of a thyroid deficiency, specifically fatigue and myopathy. Other clinical indicators of thyroid deficiency include cold intolerance, constipation, weight gain, hair loss, dry skin, bradycardia, hoarseness, and slow mental processing [32, 34]. Thyroid hormone replacement typically begins after serum cortisol levels are within normal limits [8].

Hypogonadism has been associated with adverse effects on reproductive functioning, including infertility, decreased libido, and impaired sexual function. Clinical symptoms of hypogonadism specific to women include amenorrhea, osteoporosis, and premature atherosclerosis. Testosterone deficiency in men is associated with decreased muscle and bone mass, erythropoiesis, hair growth, decreased energy, and impaired exercise tolerance [116]. If left untreated, hypogonadism can cause premature mortality secondary to cardiovascular disease [118]. Improvements in sexual function, libido, and muscle and bone formation have been reported with testosterone replacement in men [119, 120], and estrogen replacement has been associated with improved cognitive functioning in women [121, 122].

Untreated adult-onset GHD presents clinically as abnormal body composition, specifically decreased muscle mass [123], altered bone metabolism [124], and greater body fat [38, 125] in conjunction with decreased exercise capacity [113, 126], fatigue [125], low energy [77, 127], increased insulin resistance [125], unfavorable lipid profile [38], and decreased QoL [128]. Due to its adverse effects on metabolism and cardiovascular function [129], GHD may increase the risk of mortality [30, 118, 130, 131]. After GHD has been diagnosed, GH replacement is warranted. GH replacement in adults without TBI has been shown to improve body composition through decreased waist circumference [125], increased muscle mass [132], improved metabolic profiles [125], and improved cardiac function [133].

TBI as a Chronic Disease: GH Replacement Therapy

As more is learned about PTH, the previously held concept that trauma induced physical impairment of the pituitary, resulting in hormone deficiency, is beginning to change. The new concept is centered on the hypothesis that a percentage of the population is at risk to develop a chronic disease process, most likely inflammatory, in the brain after trauma of varying degree. Much like any chronic disease, the manifestations of this chronic disease can vary across a spectrum of signs and symptoms as can the severity of the presentation. Therefore, pituitary dysfunction is one of the manifestations of the chronic disease process, and GH is the most common hormone affected.

This concept is supported by several studies that show a benefit with GH replacement in patients with abnormal GH secretion by stimulation testing, but without a classical diagnosis of GHD [9, 113]. As mentioned above, a stimulation test is used to diagnose GHD, since GH is secreted from the pituitary in sporadic bursts, and many times GH blood levels are undetectable. Glucagon given intramuscularly (i.e., GST) will stimulate GH release as will insulin-induced hypoglycemia (i.e., ITT). A response of GH of less than 3 ng/mL is considered GHD, while a response between 3 and 10 ng/mL is considered an intermediate response. A response of greater than 10 ng/mL is considered normal without evidence of GHD [21]. In the studies mentioned above, patients demonstrated a positive response to GH if their response to the GST was abnormal (i.e., less than 8 ng/mL). This is in keeping with a process whereby there is a spectrum of GH response to stimulation and not a simple all-or-nothing phenomenon. The mechanism underlying a chronic disease process resulting in abnormal GH secretion is unknown.

Patients typically present to healthcare providers with symptoms that can be classified into one of two categories: fatigue or cognitive dysfunction. The fatigue associated with TBI, as mentioned above, is profound and causes life changes for the patient. Because the patient cannot manage their symptoms related to fatigue, they may decide on making major life changes, such as retire from employment, work on a part-time basis, or seek a different vocation altogether that better fits their experience of fatigue. Fatigue symptoms typically do not fluctuate as they are persistent and all consuming. Reports of sleep disturbance are also common. Cognitive dysfunction, on the other hand, centers around three main complaints: (1) loss of short-term memory, (2) slowed processing speed, and (3) executive dysfunction. We named this syndrome Brain

Injury–Associated Fatigue and Altered Cognition (BIAFAC). When these patients are tested with GST and found to have abnormal GH secretion, replacement with GH can significantly improve their symptoms. Typically, symptoms related to fatigue are the first to improve within 2–3 months following initiation of GH replacement, whereas cognitive impairment can show signs of improvement 3–4 months post-GH treatment. Functional and cognitive symptoms can continue to improve up to 1 year following initiation of GH replacement; however, continued improvement is minimal. Cessation of GH replacement therapy will typically revert symptoms to baseline [68]. Studies are currently underway to understand the potential mechanisms causing BIAFAC and how GH is able to significantly improve the symptoms experienced by these patients.

For adults, very low levels of GH are used as replacement doses. For men and postmenopausal women, the maximum daily dose is 0.6 mg/day. For reproductive age women, 0.8 mg daily is the maximum dose. Initiation of GH replacement is usually tapered over time to prevent significant edema from the GH. A standard paradigm is to start with 0.2 mg daily for 2 months and then increase to 0.4 mg daily for 2 months and finally treat with 0.6 mg daily. Serum IGF-1 levels can be monitored with the dose increases to make certain that too much GH is not being given. The studies done with GH replacement used 400 ng/ml as an upper limit assessment of GH replacement without any significant side effects [9]. The side effects of low-dose GH replacement are few. For instance, patients may complain of generalized aches in their joints. Reducing the GH dose will usually relieve these symptoms. Carpal tunnel syndrome is a major concern, but carefully discussing the symptoms with the patient and lowering the GH dose if symptoms occur will minimize any need for surgical intervention. Insulin resistance is a concern, but its possibility is minimized with the low doses of GH used. If a patient develops cancer while on GH replacement, stopping the GH replacement is recommended, although there are no studies to our knowledge that address this concern. If this is a chronic disease process, there is the possibility that the disease can improve, and patients will not need GH replacement. GH "holidays" can be taken by patients to see if the symptoms return or whether they no longer need the GH to relieve symptoms.

Within the last decade, there have been select case reports and empirical studies that have assessed the influence of GH replacement in patients, particularly with moderate-to-severe TBI (Table 1). The findings from these more recent studies are promising and support the use of GH replacement as a treatment for cognitive, psychiatric, and physical/functioning impairment post injury. In their case series study of 6 patients with GHD and moderate-to-severe TBI, Maric and associates reported improvements in psychological, social, and cognitive functioning following 6 months of GH replacement [68]. Further, these cases were re-assessed 12 months after discontinuation of GH replacement. In the 4 (out of 6) patients that received GH replacement, declines were noted in self-reported symptoms related to depression, whereas more variable findings were noted on a brief, multidimensional, self-report personality inventory designed to screen a broad range of psychological problems. There was a noted worsening of symptoms following cessation of GH replacement in three dimensions of the personality inventory, including interpersonal sensitivity, anxiety, and paranoid ideation. Of the 2 patients who did not receive GH replacement, one did not demonstrate any significant changes, whereas the other demonstrated a significant increase in psychological symptoms on multiple psychiatric parameters. As for cognitive test performances, modest improvements for those patients receiving GH replacement were noted on tasks that assess verbal memory, nonverbal memory, confrontation naming, and executive functions, but not on a test of cognitive flexibility. In their case series study of 13 patients with moderate-to-severe TBI (including children, adolescents, and adults), Devesa and coauthors reported both cognitive and motor improvements with those patients with moderate TBI, demonstrating more prominent changes following GH

Table 1 Active growth hormone (rhGH) replacement studies (2010–2017)

Author(s), Journal	TBI patient sample	Title	Findings
High et al. 2010, J Neurotrauma, 27, 1565–1575 [19]	Moderate-to-severe TBI – Adult *N* = 23 (12 active rhGH; 11 placebo); All GHD or GH insufficient	Effects of growth hormone replacement therapy on cognition after TBI	Active rhGH group demonstrated significant performance improvements over time compared to placebo group on neuropsychological tests that assess memory, processing speed, executive functions, and motor dexterity and speed (dominant hand).
Maric et al. 2010, J Endocrinol. Invest., 33, 770–775 [68]	Moderate-to-severe TBI – Adult *N* = 6 (4 active rhGH; 2 control); All GHD; case series	Psychiatric and neuropsychological changes in growth hormone–deficient patients after TBI in response to growth hormone therapy	The majority of patients who received active rhGH demonstrated symptom improvement as determined by mood (depression) and personality inventories as compared to the control patients. Similarly, patients receiving active rhGH demonstrated modest improvements in neuropsychological tests that assess memory, visuoconstruction, visuomotor speed, and executive functions. Following discontinuation of GH replacement, declines in cognition with increases in mood symptoms and maladaptive personality traits were noted.
Reimunde et al. 2011, Brain Injury, 25 (1), 65–73 [135]	Injury severity unknown – Adult; *N* = 19 (GHD = 11 [active rhGH]; GH sufficient = 8 [placebo])	Effects of growth hormone (GH) replacement and cognitive rehabilitation in patients with cognitive disorders after TBI	Both groups received cognitive rehabilitation throughout the intervention. The active rhGH and control groups both demonstrated cognitive improvements over time. Within-group comparisons revealed that the active rhGH group demonstrated significant improvements in more cognitive parameters than the control group. Further, between-group comparison revealed that the active rhGH group performed significantly better on tasks that assess verbal abstraction, expressive vocabulary, verbal intelligence quotient, and full-scale IQ.
Devesa et al. 2013, Hormones and Behavior, 63, 331–344 [83]	Severe TBI – Child, adolescent, & adult; *N* = 13 (5 GHD; 8 GH sufficient); case series	Growth hormone (GH) and brain trauma	TBI patients (GHD & GH sufficient) received clinical rehabilitation and GH treatments. Each case demonstrated improvements in physical and cognitive abilities during active rhGH treatments than had been observed during clinical rehabilitation alone.
Moreau et al. 2013, J Neurotrauma, 30, 998–1006 [134]	Mild, moderate, and severe TBI – Adult; *N* = 50 (GHD = 23 [active rhGH]; GH sufficient/ insufficient = 27 [placebo])	Growth hormone replacement therapy in patients with TBI	Cognitive, ADL, & QoL assessments were performed at baseline and 12 months. A session effect was noted for all patients. An interaction effect revealed modest improvements for the active rhGH group on a task of visuospatial incidental learning and 2 out of 6 factors on a QoL inventory.

(continued)

Table 1 (continued)

Author(s), Journal	TBI patient sample	Title	Findings
Mossberg et al. 2017, J Neurotrauma,34, 845–52 [136]	Mild, moderate, and Severe TBI; *N* = 15 (all GHD [active rhGH]	Functional Changes after Recombinant Human Growth Hormone Replacement in Patients with Chronic TBI and Abnormal Growth Hormone Secretion	Peak cardiorespiratory capacity, body composition, and muscle force testing were assessed at baseline and 1 year after rhGH replacement. Additionally, standardized neuropsychological tests that assess memory, processing speed, and cognitive flexibility as well as self-report inventories related to depression and fatigue were also administered. Peak O_2 consumption, peak oxygen pulse (estimate of cardiac stroke volume), and peak ventilation all significantly improved. Maximal isometric and isokinetic force production was not altered. Skeletal muscle fatigue did not change, but the perceptual rating of fatigue decreased. Cognitive performance did not change significantly over time, whereas self-reported symptoms related to depression and fatigue demonstrated modest improvements.

GHD Growth hormone deficiency, *TBI* Traumatic brain injury, *ADL* Activities of daily living, *QoL* Quality of life

replacement and ongoing rehabilitation services [83]. High and colleagues reported on the cognitive effects of GH replacement in patients with moderate-to-severe TBI over a year [19]. In their double-blind, placebo-controlled study, 12 patients received active medication and 11 patients received placebo. Given the small sample size, both GHD and GH-insufficient patients (GST peak, 3–8 ng/mL, respectively) were grouped together. Cognitive and motor improvements for patients in the active medication group were discovered on tasks that assessed verbal learning, information-processing speed, executive functions, and motor dexterity and speed for the dominant hand compared to the control group. Similarly, Moreau and coauthors evaluated the effects of year-long GH replacement in patients with moderate-to-severe TBI compared to a brain-injured, age-matched control group [134]. Their findings revealed moderate improvements in memory (i.e., immediate memory) and information-processing speed. Improvements on tests of executive functions, attention, or language were not reported. More pronounced improvements were discovered in patients with greater levels of injury severity. In another study, Reimunde and coauthors assessed the impact of GH treatment in patients with moderate-to-severe TBI (11 active GH; 8 placebo) [135]. Following 3 months of GH replacement, they discovered improvements on tests of more crystallized skills including vocabulary, verbal intelligence quotient, and full scale IQ on the Wechsler Intelligence Scale (WAIS). Lastly, Mossberg and coauthors reported positive physical functioning and psychological changes, but not cognitive improvements, in 15 patients with mild-to-severe TBI replaced with GH for 1 year [136]. Peak $VO_{2\,max}$, peak oxygen pulse (an estimate of cardiac stroke volume), and peak ventilation were all significantly improved compared to baseline. Maximal isometric and isokinetic force production remained unchanged. Skeletal muscle fatigue did not change significantly; however, patients' self-reported rating of fatigue was reduced (statistical trend). Cognitive performance did not improve significantly, although self-reported symptoms related to depression did decrease significantly.

Conclusion

A moderate-to-severe TBI is both disease-causative and disease-accelerative [31]. There may be many other clinical manifestations of this chronic disease process that are currently uncharacterized or not fully understood. For instance, a recently published study assessed the absorption of amino acids following consumption of a nutritionally balanced meal in patients with moderate-to-severe TBI (residing in long-term care facilities) compared to age-matched, noninjured control subjects [137]. Results from their study collected in two separate facilities in different regions of the United States demonstrated that patients with TBI had abnormal levels of essential amino acids compared to control participants after a standard meal. The cause of the abnormal levels is not known, but the clinical significance of the abnormal levels could affect skeletal muscle, neurotransmitters, and metabolism. More specifically, early diagnosis and subsequent treatment can improve outcomes. However, PTH typically is not identified or treated due to masking effects of impairments secondary to damage to brain parenchyma other than the pituitary. Further, in the case of mTBI, while there is evidence of pituitary deficits, patients might not present to a physician for months following an injury or not at all. Because the chronic disease process post TBI is not clearly defined, many patients are suffering from BIAFAC, as discussed in this chapter, without the medical awareness that GH replacement is an option for management or resolution of cognitive, psychiatric, or physical/functioning sequelae. Continued research is needed to further define moderate-to-severe TBI as a chronic disease process and to increase our understanding of underlying mechanisms in order to develop treatments for improvements in functional outcomes and QoL in this patient population.

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Visual Disturbances and Mild Traumatic Brain Injury (mTBI)

Lauren C. Ditta, Nicole K. Weber, Katherine E. Robinson-Freeman, Elle McKenzie, Samantha A. Thomas, Han Jun Kim, Ansley Grimes Stanfill, and Jack W. Tsao

Background

Mild traumatic brain injury (mTBI) can occur with or without a loss of consciousness [1]. In 2001, the expert Concussion in Sport Group of the first International Symposium on Concussion in Sport defined mTBI as a complex pathophysiological process affecting the brain, induced by traumatic biomechanical forces. The classic symptoms of mTBI can be categorized into somatic, emotional, and cognitive symptoms [2]. Somatic symptoms include headaches (the most common symptom post concussion) [3], dizziness, and visual disturbances [4, 5]. Several studies in adolescent, military, and civilian populations showed that, of patients with a concussion, 60–69% of them had at least one visual symptom [3]. Emotional symptoms include irritability, anxiety, and depression. Cognitive symptoms can include difficulties with memory, attention, and processing speed (reaction time) [6]. Because of the complexity of the neural pathways involved in vision, oculomotor functioning is thought to be one of the more sensitive methods of detecting a mTBI [7].

Visual Pathways of the Brain

Changes in visuomotor performance can be one of the symptoms experienced after a concussion [8] and are quite common [3]. They can be used as determinant of mTBI, because over half the brain circuits are involved in vision and eye movements [4]. The structures of the brain concerned with the control of eye movements are well known and mapped. Studies have shown in populations with neural injury that eye movement is closely tied to the functionality of the brain [1, 9]. Changes have been seen in brain activation postconcussion, including hyperactivation and hypoactivation in certain areas of the brain. Hyperactivation may be due to compensatory strategies being employed to

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increase performance, but at the cost of efficiency [10]. Additionally, changes in event-related alpha electrical activity in the brain have been reported in individuals who have suffered from a concussion, further illustrating physiological changes in the brain [11].

Brain Damage and Oculomotor Functioning

The numerous structures of the brain that are used to plan and execute oculomotor function are thoroughly mapped and form a complex web of pathways in cortical structures, subcortical structures, and the cerebellum [1, 9]. The interdependency and extensiveness of these neural networks puts the visual system at risk during an mTBI [12]. Furthermore, studies suggest that mTBIs have a direct impact on motor control, with oculomotor functioning being the most sensitive [1, 8, 12, 13]. For example, a study done on mTBI by Heitger and coauthors [8] found prolonged saccade latencies and more directional errors in saccade tasks, as well as decreases to upper-limb movement speed and motor control accuracy.

Since a fully functioning visual system requires intact efferent and afferent neural pathways, any changes in vision caused by a TBI could indicate damage to these pathways [5]. Specific symptoms of visual dysfunction depend on whether the damage occurred within the afferent (incoming) visual pathways, efferent (outgoing) visual pathways, or the visual association (recognition) areas [14]. For example, studies using diffusion tensor imaging have shown damage to white matter fiber tracts, with areas in the orbitofrontal and anterior temporal lobe frequently being affected [3]. This is likely to be a form of diffuse axonal injury (DAI) [10], and can be associated with secondary injuries, which cause more deficits; these secondary injuries are often caused by changes in blood flow and chemical activity in the brain [3]. The specific dysfunctions found in afferent, efferent, and visual associations are discussed in more detail below and may be useful for making a diagnosis of mTBI.

Afferent Visual Dysfunction

Defects in the afferent visual system may present as a decline in acuity, color differentiation, contrast sensitivity, or a defect in the visual field as a result of direct trauma to the optic pathway [14]. In the setting of direct trauma to the optic nerve, the pupil response may be sluggish, or there may be the presence of an afferent pupillary defect [14]. Midline shift, another reported symptom, is a sense of a shifted center of vision where patients perceive a warping of their vision so that objects on one side of the visual field appear closer than objects on the other side, which appear farther away from them [14, 15]. Patients may also suffer from visual attention deficits. Healthy patients are able to focus on specific objects in a cluttered environment; however, patients with mTBI can have impaired attention and difficulties filtering out irrelevant information in a complex visual scene [16]. Further, visuoperceptual scene processing, visual working memory, and visual attention efficiency can be affected detrimentally by concussions, as illustrated by hyperactivity in certain brain regions such as the orbitofrontal region and right hippocampus [10]. Deficits in visual acuity, contrast sensitivity, and color vision occur most commonly [3, 17, 18].

Efferent Visual Dysfunction

Efferent visual deficits may include decreased accommodation and convergence amplitudes, diplopia, nystagmus, slowed pupillary reactions, and a reduction in pursuit ability [14]. Deficits in accommodation most commonly present as difficulty in focusing at distance, but more so at near vision. Convergence, which drives the eyes in opposite directions (bilateral adduction of the eyes) to maintain the image of an object on the fovea, can also be reduced. This may result in convergence insufficiency [4, 19], which was shown to occur in 42% of individuals after a sports-related concussion according to one study [3]. Patients may experience eye strain (asthenopia), headache, or reduced stereopsis (depth perception) as a result [20]. As a separate entity, patients may develop convergence

paresis [21], with an inability to maintain binocular fusion, particularly at near vision. Nystagmus, the rhythmic involuntary movement of the eyes, often causes oscillopsia and degraded vision [22]. Slowed pupillary responses commonly result from increased intracranial pressure, which is witnessed after a severe TBI, not an mTBI; however, decreased responses are also reported in cases of mTBI when increased intracranial pressure is not usually found [14]. Eye movement issues are prevalent in patients who experience a concussion; 90% are reported to suffer from an issue with eye movement. Of these issues, conjugate eye movement is commonly found to be altered; however, problems seen may vary by the severity of the injury that is experienced [3]. Smooth pursuit, another part of the supranuclear ocular motor pathway, can be affected by mTBI [20]. One study showed scores on a visual tracking task were worse for those suffering from a concussion [3]. Patients may also see a change in saccadic movement [3], as discussed later in this chapter. The ability to anticipate the future location of a target during a repetitive motion is also limited in patients with mTBI; an example case study is presented toward the end of this chapter [23, 24].

Visual Association Area Dysfunction

The visual association areas surround the primary visual cortex, receive signals from the visual cortex, and interpret them as recognizable objects [25]. Damage to this area can cause difficulty in recognizing objects. Even if the shape and color are still seen, the object cannot be recognized as a functioning whole. This can cause laborious reading, which can result in losing one's place and the inability to restate what was read [14, 26]. Reading impairment can last for an extended period of time; one study reports performance decreases still prevalent at 6 months post injury, and even still at 12 months post injury in older patients [3]. Furthermore, visual impairments along these lines can occur, if rarely, such as prosopagnosia, where individuals can no longer recognize faces, or Balint's syndrome, the symptoms of which include ocular apraxia and optic ataxia [3]. Additionally, pursuit eye movement has been suggested as a way to test for cognitive functioning [3]. Therefore, these deficits are considered as possible symptoms of mTBI and could be used to assist in the diagnosis.

Visual Tracking with Conventional Eye Movements

Frequent difficulties with focusing and attention are common symptoms of mTBIs; however, most neuropsychological measures are relatively insensitive to lapses in concentration. Most of the existing tests only measure attention for discrete events and do not measure prolonged attention [27, 28]. Visual tracking, on the other hand, requires continuous attention over time and can also be sensitive to deficits caused by a head injury [1, 29]. Visual tracking requires both smooth pursuit movements and saccadic elements, thus integrating sensory inputs and conscious motor efforts to be used as an objective functional marker of injury [1]. Visual tracking tests can also incorporate higher cortical functioning in areas that may have changes from mTBI, such as language processing and speed [4]. Furthermore, rapid automatized naming (RAN) tests [30] and video-oculography (VOG) have been shown to measure ocular functioning and illustrate the underlying changes in processes and neurophysiological changes [31]. Listed in Table 1 are the common eye movements that are used in the testing of a concussion and the anatomical pathway affected.

Saccades

There are several types of saccades that are important to consider in mTBI. Prosaccades are the rapid saccades toward a target [32]. These are stimulus driven, and as such are usually classified as a reflexive movement. Saccades that are involuntarily generated to an unexpected visual target are specifically termed reflexive visually guided saccades [4, 33] and

Table 1 Major eye movements and anatomical pathways involved

	Purpose	Anatomical pathway	Clinical tests to assess
Saccades	Rapidly shifting horizontal gaze	Reflexively generated from the parietal eye field or intentionally generated in the frontal eye field, then sent directly to the contralateral PPRF or via the superior colliculus. The PPRF then generates horizontal saccades	Fixate on a peripheral target and then a central object, such as the examiners nose
Pursuit	Follow slowly moving objects	Descending pathways from tempero-parieto-occipital junction and frontal eye fields connect in the pons and innervate the cerebellum, which then excites the sixth cranial (abducens) nerve nucleus	Track a moving object at no more than 30° per second
Vestibulo-ocular reflex	Stabilizes images on the retina by producing eye movements in opposite direction to head movements	Semicircular canals signal to vestibular nuclei, which excite the sixth cranial (abducens) nerve nucleus	Quick head thrusts while fixating
Vergence	Simultaneous movement of eyes in opposite directions to maintain fusion on objects near or far	Cerebro-brainstem-cerebellar pathways. Not well understood	Measure NPC, assess for phorias with cross-cover test, measure fusional amplitude with base-out prism test

Used with permission of Elsevier from Ventura et al. [19]
PPRF paramedian pontine reticular formation, *NPC* near point of convergence

are primarily controlled by the superior colliculus [20]. In contrast, antisaccades are saccades directed in the opposite direction of a presented visual target; thus, antisaccades require the suppression of a reflexive saccade toward the visual target [1, 4, 34]. In smooth pursuit movements, the saccade is a continuous slow movement with the eyes fixed on the moving target. This type of saccade is under voluntary control and requires an active motor input [1, 32]. Another type of saccade used for visual tracking is memory-guided saccades, where saccade generation is directed toward the location of a previously present visual target [1, 12]. Memory-guided or volitional saccades to a target are controlled by several areas of the cerebral cortex, including the premotor zones that project to the frontal eye fields [20]. Figure 1 shows the process of control of saccade generation and inhibition through the major cortical areas. Several changes in saccadic behavior have been noted in persons with concussions, including an increase in errors when looking to a target, reduced amplitudes, both slower and longer saccades, and a deficit in the ability to track a moving target, as well as a decrease in the self-paced saccades individuals initiated. Additionally, one study showed that patients had both increased areas of the brain being recruited and increased activation [3].

Utilizing the Visual Pathways

Subtle changes in visual tracking can be a biomarker for mTBI. Patients with mTBI have been found to have more impairment in memory-guided saccades and antisaccades. These include increased saccadic latencies, larger directional errors, and worsened spatial accuracy [4]. These subtle changes in visual tracking can be utilized in rapid detection of mTBI.

Rapid Sideline Detection

The early and rapid detection of mTBI is an important factor in preventing further damage. Not only do we want to maximize complete recovery from any mTBI, but we also want to minimize the risk of having a second concussion while still recovering from the first. This is known as Second Impact Syndrome (SIS). In SIS, the

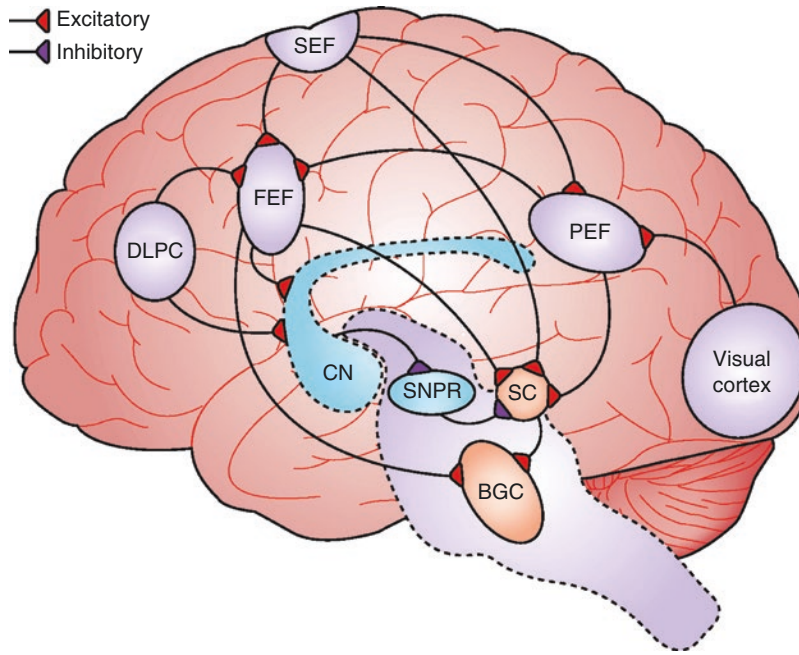

Fig. 1 Major cortical areas in control of eye movements and visual processing, with projections illustrating saccade generation. The frontal, parietal, or supplementary eye fields (FEF, PEF, SEF) send signals to begin saccades to the superior colliculus (SC). The SC then projects to the brainstem gaze centers (BGC). The FEF also sends direct signals to the BGC to initiate saccades. However, the substania nigra pars reticulata (SNPR) can inhibit the SC to prevent saccade generation. If the frontal eye fields are activated before saccade generation, the SNPR can be inhibited by the caudate nucleus. There are multiple pathways that can be used to generate saccades. The FEF primarily generates voluntary or memory-guided saccades; the PEF generates reflexive saccades; the SEF generates saccades in coordination with body movements and generates successive saccades via pathways through the FEF, PEF, and SC. The dorsolateral prefrontal cortex (DLPC) controls antisaccades, the inhibition of reflexive saccades, and the advanced planning of saccades. (Used with permission of Elsevier from Ventura et al. [19])

brain swells rapidly following the second head impact, resulting in potentially fatal or severely debilitating consequences [35].

Preventing SIS is especially relevant for athletes. Players who have already suffered one concussion are three times more susceptible to another concussion [35]. This makes it imperative that players are removed immediately and evaluated upon the first injury and that they do not return to play until recovery is complete.

Another similar, but clinically distinct, syndrome is Post Concussion Syndrome (PCS), which is defined as prolonged symptoms persisting for longer than 3 months in the mTBI patient following the initial injury [5]. Patients with these syndromes have been shown to have lingering visual impairments in antisaccades, memory-guided saccades, and self-paced saccades when compared to patients who recovered from mTBI [1].

It is likely that many initial concussions go undetected or unreported [36]. This increases risk to the athlete of secondary head injury, and of increased or persistent symptoms. Physical and cognitive rest is critical to ensuring long-term health. Therefore, early detection of concussion following head injury is vital in order to allow for appropriate return-to-play decision-making after recovery is complete.

King-Devick Test® (K-D Test) (King-Devick Technologies, Oak Terrace, IL, US)

The King-Devick (K-D) test is a saccade test administered on three test cards with an additional demonstration practice card [37], as shown in Fig. 2. The participant quickly reads

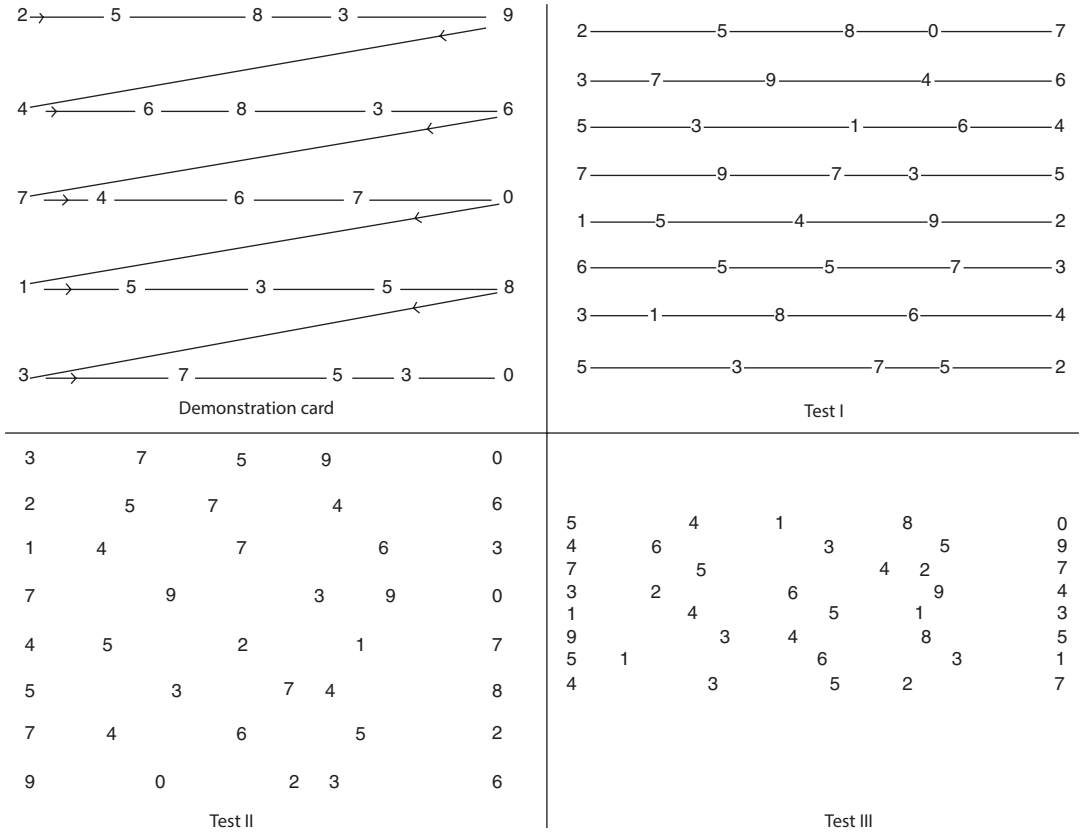

Fig. 2 The demonstration and test cards for the King-Devick® (K-D) test (King-Devick Technologies, Oak Terrace, IL, US), a rapid sideline screening test for sports-related concussions. This can be used as an early determinant for mTBI by utilizing the injury's effects on eye movements. (Used with permission of Wolters Kluwer from Galetta et al. [39])

aloud eight rows of single digit numbers. The time taken to complete the test is recorded as well as the number of errors made. The test integrates not only eye movement and attention, but also incorporates language function, and so requires the coordinated use of the brainstem, cerebellum, and cerebral cortex [38, 39]. The integration can then be used to detect suboptimal brain activity following a concussion [13, 39, 40] by comparing a postconcussion test to that of a baseline test taken by the same athlete.

The test is available either as note cards or on handheld tablets. Either of these makes the test highly portable and easy to use on or away from sidelines [38]. The tablet computer has one advantage over the note cards, as the numbers within the K-D test do change so that athletes cannot memorize a set of numbers at baseline to perform when a concussion occurs [39].

As mentioned, all athletes should undergo testing before and after a practice or a game even if there is no witnessed hard-hit or collision. This allows baseline comparisons to be made. Many athletes may fail to report symptoms, because they do not want to be removed from play; even with proper education, athletes are still hesitant to report symptoms [41]. Furthermore, there is the incorrect assumption among athletes that concussions are not serious injuries, since they occur often [35]. The K-D test is useful not only in quickly identifying if an athlete had a suspected concussion, but it can also identify players who have impactful head injuries but did not show or

report any symptoms of a concussion [42]. This has implications for all contact sports, where not every injury is witnessed, and concussions can occur without a direct blow to the head.

Still, the K-D test is only meant to be used as a rapid sideline test to detect the possibility of a concussion but is not necessarily diagnostic of one. If a person is thought to have a concussion, he or she should seek medical attention. Currently, there is no composite test that can be used to diagnose a concussion [39].

An important note to consider about the K-D test is the presence of a learning effect (practice effect). Upon repeated administrations of the test, the time taken to complete it decreases significantly—that is, the score improves [37]. Thus, to account for these effects during baseline assessments, the test is usually administered twice, with the better score and fewer errors used as the comparison score.

Despite this, the K-D test does have some marked advantages. Administration of the test can be done by nonmedical athletic personnel without compromising the precision of the test [43]. Furthermore, the K-D test is not affected by physical fatigue. After routine practices and exercises, players who were not concussed did not show worsening results on the test. In fact, nonconcussed athletes actually performed better than their baseline assessment [36]. This regular learning effect observed in the K-D test emphasizes the fact that any worsening score is a strong indicator of a concussion.

In one study, the K-D test was administered to MMA and boxers before and after fights to test its reliability for detecting changes following head trauma and concussions [39]. In addition to the K-D test, the military acute concussion evaluation (MACE) was also given to compare with postfight scores. Postfight K-D scores were significantly higher (worse) for those with head trauma during the match, suggesting that the K-D test is a reasonable method for identifying athletes with head trauma. One of the aspects assessed by the K-D test is eye movement, and, as such, these results provide further support for the importance of visual changes post concussion.

Eye Movement Control

Several recent studies have investigated the impacts that sustaining a concussion may have on individuals, with particular emphasis on the visual changes that may co-occur with this injury. The various studies focused on different aspects of visual changes, but all found changes to be related to sustaining a concussion. In one such study focused on the control of eye movements, patients with mTBI were asked to visually track moving targets [6]. Patients sat 126.4 cm away from the screen that presented the visual-tracking task. The first task was to track a red disk–shaped target that moved clockwise continuously in a circle. In the second task, patients were asked to complete the same task, except this time the target would disappear at random points and then reappear on the same projected path. The patient was asked to predict the position of the target's reappearance, and all of the patient's eye movements were recorded.

The findings in this study indicate that the gaze of mTBI patients lagged behind the target after it reappeared, meaning there was an abnormality in smooth pursuit eye movements. The deficits seen were even more pronounced when the tracking target was occluded for varying periods of time (i.e., the tracking stimulus disappears for a portion of the repetitive course, then reappears further down the course) [23]. Thus, using gap-detection methods may prove to be an even more sensitive measure than just visual tracking on its own.

Further, another study found changes related to gaze stability. Ten collegiate athletes with concussions and ten controls completed two trials of an "antisaccade" postural control task on the Wii Fit Soccer Heading Game. The participants were asked to minimize their gaze movement and look at the middle of the screen, while their eye movements were tracked. The results of the experiment show that athletes with concussions had a significantly larger "gaze resultant distance," defined as the square root of the sum of the changes in horizontal and vertical coordinates squared. This could indicate that a deficit in gaze stability could be used to detect concussion [44].

In addition to these changes in gaze control and stability, the influence of concussions on visual-motor-tracking force complexity was assessed; 35 participants who had a history of concussion were compared against 15 controls without a history of concussion on a visual-motor-tracking task. Results illustrated that with an increase in the number of concussions, there was a decrease in visual-motor-tracking force. This effect was further influenced by gender and loss of consciousness history [45].

The above-mentioned studies all point to visual changes being viable and important indicators of concussion, but one study implemented both self-reported measures of changes in vision and empirically measureable visual changes to assess if there were differences between these types of measures. Capó-Aponte and coauthors conducted a case-control study in which they compared performance on several tests, including pupillary light reflex (PLR), near-point convergence (NPC) break, King-Devick test (K-D), and the Convergence Insufficiency Symptom Survey (CISS) between individuals with a diagnosed concussion or those without a concussion diagnosis. It was found that all tests were significantly different between groups, and as such, the authors suggested that the average dilation velocity (ADV), average constriction velocity (ACV), and NPC could be used as biomarkers to detect and diagnose concussions, and that such measures should be used above self-report measures [7]. These results, suggesting the validity of using visual changes as a more reliable, empirical measure of concussion, are in accordance with several of the studies cited here. Providing further evidence that objective measures, such as the NPC and CISS mentioned above, are better at assessing visual changes and symptoms, a study on children and adolescents before and after concussions showed that these scores were detrimentally affected, and showed the effects of the concussion, even if the children were not able to detect visual changes and did not report them on self-report measures. This study also reported visual changes to be both prevalent and severe in females [46]. Showing further support for these kinds of measures in concussion testing, a recently published study investigated the use of eye tracking via the Eyelink 1000 eye tracker in concussion testing. The investigators analyzed several measures of visual dysfunction in both concussed and nonconcussed children, including conjugacy of eye movements, convergence, and accommodation, and found that abnormalities in these areas were detected by the eye-tracking software, and that they were related to concussion symptoms, further supporting the use of these measures in concussion testing [47].

Electroencephalography

Looking beyond these types of measures of visual changes, one study implemented electroencephalography (EEG) recordings to look at brain electrical activity in relation to a visual task; 13 athletes with a history of multiple concussions were matched to 14 nonconcussed athletes, with both groups completing a visual-spatial attention task while having cortical alpha activity recorded. This study showed that the concussed group differed from the nonconcussed group in terms of the amplitude of the alpha waves and alpha activity. Those who had a history of concussion demonstrated fewer event-related perturbations due to stimuli, and overall activity related to events was correlated to the number of concussions sustained. Because large changes in alpha activity in response to events are thought to be reflective of cognitive efficiency, individuals who have experienced a concussion have cognitive abilities relating to visual-spatial attention affected by the concussion. This effect seems to be long-lasting after the time of injury, as the average time since injury in this study was 30 months [11].

Conclusion

The results of these studies all implicate visual changes as reliable indicators of concussions, both in adult and pediatric populations. Because of their empirical nature, studies stated that they were more reliable than self-report measures

that are often a part of the concussion assessment. This is particularly important in concussion testing, as it is a common injury in pediatric populations, where the patients may not be able to fully report the changes that they are experiencing, as well as in athletes, where there are external motivations that prevent individuals from honestly and accurately reporting their symptoms. Effective means of detecting concussion is needed, so it is clear that the connection between concussion and visual changes, as well as the utility of implementing measures of these changes in concussion testing, should bear further investigation.

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Mild TBI and Co-Occurring PTSD Symptoms in Service Member Populations

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Abbreviations

AOC	Alteration of consciousness
ART	Accelerated Response Therapy
CAPS	Clinician Administered Posttraumatic Stress Disorder Scale
CBT	Cognitive Behavioral Therapy
CPG	Clinical Practice Guideline
CPT	Cognitive Processing Therapy
DoD	Department of Defense
DoDI 6490.11	Department of Defense INSTRUCTION 6490.11
DVBIC	Defense Veterans Brain Injury Center
EMDR	Eye Movement Desensitization and Reprocessing
GCS	Glasgow Coma Scale
GWOT	Global War on Terror
LOC	Loss of Consciousness
MACE	Military Acute Concussion Exam
mTBI	Mild Traumatic Brain Injury
OEF	Operation Enduring Freedom
OFS	Operation Freedom's Sentinel
OIF	Operation Iraqi Freedom
OIR	Operation Inherent Resolve
OND	Operation New Dawn
PCL	Posttraumatic Disorder Checklist
PE	Prolonged Exposure Therapy
PTA	Posttraumatic amnesia
PTSD	Posttraumatic Stress Disorder
SAC	Sideline Assessment of Concussion
TBI	Traumatic Brain Injury
VA/DoD	Veterans Health Administration/Department of Defense

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Introduction

Since 2001, over two million service members have deployed in support of ongoing conflicts overseas. These conflicts have placed service members at increased risk for experiencing traumatic events as well as injuries by blasts,

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vehicle crashes, and other war-related dangers. The 2008 Rand report [1] was the first to highlight traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) as the "signature wounds" of the ongoing wars in Iraq and Afghanistan. The report estimated that of 1.64 million service members deployed in support of Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF) from the beginning of the conflict through October 2007, 300,000 individuals were suffering from PTSD or depression and 320,000 had sustained a probable TBI during their deployment.

Since that report, OIF/OEF have ended, Operation New Dawn (OND) began and ended, and new conflicts have begun: Operation Freedom's Sentinel (OFS) and Operation Inherent Resolve (OIR). Additionally, thousands of service members have been deployed worldwide in support of the Global War on Terror (GWOT). Numerous studies since then have continued to examine the incidence of TBI and PTSD among service members, contributing to our understanding of TBI and PTSD, both individually and when the disorders co-occur. From these epidemiological studies, we have learned that incidence of TBI and PTSD in the service member population is not solely war-related. An increased emphasis on screening and identification has captured an increased incidence of both TBI and PTSD unrelated to combat [2].

A complete literature review of all aspects of TBI and PTSD is beyond the scope of this chapter. Rather, this chapter serves to provide an overview of mild TBI (mTBI) and PTSD in service member populations, our current understanding of their interaction with one another, the current diagnostic criteria for both, and highlights the empirical treatments for both disorders and provides recommendations for future directions in understanding the interaction between mTBI and PTSD.

What Is TBI?

As defined in the Department of Veterans Affairs/Department of Defense (DoD) Clinical Practice Guidelines, revised in 2016: *A traumatic brain injury (TBI) is defined as a traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force and is indicated by new onset or worsening of at least one of the following clinical signs immediately following the event*: loss of consciousness, alteration of consciousness, loss of memory for events immediately before or after the injury, alteration of mental status at the time of the injury, neurological deficits, or intracranial lesion [3]. The classification of TBI severity is based on a thorough history and physical examination performed as soon as possible following the event. See Table 1.

Mild traumatic brain injury (mTBI) and concussion are terms that, for these purposes, are used interchangeably [4]. Symptoms associated with post-mTBI fall into three general categories. These include physical, cognitive, and emotional symptoms. Physical symptoms may include sleep disturbances, headaches, nausea, dizziness or balance problems, nausea/vomiting, sensitivity to light and

Table 1 Classification of TBI Severity. (If a patient meets criteria in more than one category of severity, the higher severity level is assigned)

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness (LOC)	0–30 minutes	>30 minutes and <24 hours	>24 hours
Alteration of consciousness (AOC)	Up to 24 hours	>24 hours; Severity based on other criteria	
Posttraumatic Amnesia (PTS)	0–1 day	>1 and <7 days	>7 days
Glasgow Coma Scale[a] (GCS)	13–15	9–12	<9

Source: U.S. Department of Veteran Affairs, Department of Defense [3]

[a]In April 2015, the DoD released a memorandum recommending against the use of GCS scores to diagnose TBI. See the memorandum for additional information. (Memorandum from the Assistant Secretary of Defense (Health Affairs). Traumatic Brain Injury: Updated Definition and reporting. 6 April, 2015. U.S. Department of Defense, Washington, DC)

sound, tinnitus, and fatigue. Cognitive symptoms may include problems with memory, attention/concentration, processing of information, and executive function. Emotional/behavioral symptoms may include increased irritability, mood swings, symptoms of depression, and anxiety [3].

Individuals who sustain a single mTBI/concussion typically return to baseline function within hours to days without residual effects. The World Health Organization Collaborating Center Task Force on mTBI, based on meta-analysis, suggested that most (these need numbers) adults with uncomplicated mTBI have good outcomes and generally a full recovery within months [5]. More recent research, including that conducted by Mac Donald and colleagues [6], indicated that a significant number of individuals with concussive blast TBI experienced persistent postconcussive symptoms (PPCS) compared to individuals without TBI. Worsening of symptoms for these individuals was noted on measures of PTSD and depression, but not on cognitive measures. For those individuals, whose symptoms continue, the overlap between symptoms of mTBI and other frequently co-occurring conditions, including depression, anxiety, and sleep disturbances, as well as PTSD, can make both diagnosis and treatment more challenging.

mTBI Prevalence

mTBIs make up the majority of TBIs sustained in both civilian and military populations. Among the service member population, mTBIs specifically are the most common type of traumatic injury [7]. In 2013, a total of approximately 2.8 million TBI-related emergency department visits, hospitalizations, and deaths occurred in the United States, and most were mild in initial severity [8–10]. Similarly, per the Defense and Veterans Brain Injury Center (DVBIC) [11], the majority of TBIs sustained by service members are classified as mTBI. Since 2002, 361,092 service members have sustained brain injuries, 82.4% were classified as mTBI [11]. Most service members who sustain an mTBI are able to return to full duty within a week to 10 days [11].

Most mTBIs that take place in the service member population are actually noncombat related. According to Brundage and coauthors [2], war zone service only accounted for one of seven postdeployment TBI diagnoses between 2003 and 2005, half of all such diagnosis in 2007–2009, and only one-third of diagnosis between 2012 and 2013. It is important to note that the prevalence estimates simply focus on counting whether an mTBI occurred and do not provide any information on what the current symptoms or level of impairments are present in those individuals who did sustain an mTBI [12].

Management of mTBI

In 2016, the VA/DoD Clinical Practice Guideline (VA/DoD CPG) [3] for the Management of Concussion-Mild Traumatic Brain Injury was revised based on a *systematic review of both clinical and epidemiological evidence* by a panel of multidisciplinary experts. It was anticipated that the use of the guideline will vary based on the individual needs of the patient, the settings, and the available resources.

The VA/DoD CPG [3] outlines terms used to indicate the postinjury periods following mTBI as:

- Immediate period refers to 0–7 days post injury
- Acute period refers to 1–6 weeks post injury
- Post-acute period refers to 7–12 weeks post injury
- Chronic refers to >12 weeks post injury

In addition to the CPG, the DoD has specific guidelines for the management of mTBI/concussion in the deployed setting [13], where it must also be acknowledged that the circumstances involved in assessing an mTBI may well be complicated by mission demands, other physical injuries, or traumatic events. Once a person has been flagged for an assessment to investigate the impact of head trauma, the DoDI 2012 guidelines are summarized as follows. Service members involved in a potentially concussive event will be referred for a medical evaluation if they report a "yes" response on the

injury, evaluation, and distance checklist. MTBI/Concussion Screening and Initial Evaluation should also include the completed Military Acute Concussion Evaluation (MACE) [14].

A tool that can be utilized by first responders, derived from the Sideline Assessment of Concussion (SAC), frequently used on college and professional football players, is the Military Acute Concussion Evaluation (MACE) [14]. The MACE can be administered in approximately 15 minutes and comprises three main sections: history, screening neurological examination, and cognitive evaluation. The history section asks the provider to obtain a description of the incident, cause of the injury, determining the presence or absence of a helmet, investigation of anterograde and retrograde amnesia, and LOC. The neurological examination assesses ocular (papillary response and eye tracking), verbal (speech fluency and word finding), and motor (pronator drift and gait and coordination) functions. The cognitive portion includes an assessment of orientation to various factors of time, immediate memory, brief neurological screening, recalling digits backwards, and a delayed recall of the items on the immediate memory word list. There are three possible outcomes for the MACE: (a) no concussion, (b) concussion with LOC, (c) or concussion with no LOC [14]. A diagnosis of concussion can be made from the history section alone.

When possible, these DoDI guidelines for use in a deployed setting require that a service member who has experienced a concussive event rest for 24 hours, beginning at the time of the event and be monitored for any potentially worsening symptoms (e.g., worsening headache). If the service member has two diagnosed mTBI/concussions that occurred within the past 12 months, return to duty is delayed for an additional 7 days following symptom resolution. If the service member has three diagnosed mTBI/concussions within the past 12 months, return to duty is delayed until a recurrent concussion evaluation has been completed by a neurologist. The recurrent concussion evaluation includes a comprehensive neurological evaluation, neuroimaging, neuropsychological assessment including the domains of attention, memory, processing speed, and executive functioning, a functional assessment, and duty status determination. For the complete guidelines for management of mTBI in the deployed setting, please refer to the DoDI 6490.11 [13].

In circumstances where the assessment of the TBI is taking place >7 days from the TBI event, the process of assessment is similar in that it is based upon physical examination and history. The clinician needs to rule out or identify urgent/emergent conditions that require referral to emergency care or further evaluation and treatment, and assess for the level of severity of traumatic brain injury. The MACE, while required for use in the deployed setting, is considered less useful in identifying the cognitive symptoms associated with the diagnosis of mTBI, with lower sensitivity and specificity, when administered at a more distant time from the traumatic brain injury event [15]. If the level of severity is determined to be an mTBI, the individual will be monitored for the possibility of worsening symptoms and advised to rest and avoid risk of further brain injury. The individual should be educated on the symptoms and expected recovery of mTBI.

For those individuals with a history of mTBI whose symptoms persist beyond the immediate period, >7 days, or whose symptoms present at a later time remote from the incident, the VA/DoD CPG recommends that the primary care provider should *establish a therapeutic alliance with the patient, complete a physical examination, history, mental status exam, psychosocial evaluation, and explore symptom attribution* [3]. The individual with a history of mTBI and their family should also be educated on the expected, positive, recovery pattern of mTBI. The individual with mTBI should be evaluated for co-occurring conditions such as PTSD, depression, sleep disturbances, pain, or substance abuse problems. The VA/DoD CPG recommend initiating symptom-based treatment and implementing early interventions. Early interventions include, in addition to education on the expected recovery pattern of mTBI, the prevention of further injuries, sleep hygiene education, relaxation techniques, avoidance of caffeine, tobacco, and alcohol, and monitored, progressive, return to normal function.

If symptoms do not resolve in 90 days, the VA/DoD CPG recommends re-evaluation for cognitive or neuropsychological performance to determine functional limitations and initiation of symptom-based treatment. The VA/DoD CPG does not recommend any specific battery of neuropsychological tests but does recommend that the following domains be evaluated – memory, attention, processing speed, and executive functions – and that formal measures of effort and validity testing be included. The VA/DoD CPG further recommends that these individuals who present with reported cognitive changes be referred to cognitive rehabilitation therapists with expertise in TBI.

What Is PTSD?

PTSD is diagnosed based upon patient report of clinical symptoms. To meet current diagnostic criteria in the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) following exposure to trauma, patients are required to demonstrate symptoms for a minimum of 1 month from 4 symptom clusters: (1) intrusion symptoms, such as recurrent distressing memories or dreams; (2) persistent avoidance of stimuli connected to trauma; (3) negative thoughts or emotions connected to the traumatic events; and (4) changes in activation such as startle or sleep patterns following trauma [16]. The cluster of negative thoughts, an addition to the diagnostic criteria from the previous Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM–IV), is thought to reflect thinking that PTSD represents a disorder in reactivity [17] and that revised diagnostic criteria are reflective of changes in overall levels of arousal and awareness thought to be central to the disorder [18].

Although diagnosis is based upon symptom history, there are a number of clinical scales available for monitoring PTSD. The most accurate scales for determining the presence and severity of PTSD are clinician-administered scales, such as the Clinician Administered Posttraumatic Stress Disorder Scale (CAPS) [19]. Although these scales are the gold standard for research, they require administration by a clinician trained in their use and in-depth discussion of traumatic events, which can often be activating for subjects. As such, they are generally used only for research, not to screen for illness or clinically monitor patients. For clinicians seeking a means to screen for PTSD in a clinical setting, there are a number of brief scales with between 4 and 20 questions that have established efficacy for the detection of PTSD [20]. Most of these, however, were validated against earlier DSM-IV criteria and, while still used clinically, their efficacy has not been established against the newly revised DSM-5 diagnostic criteria. Presently, there is only one patient-administered screen validated against the CAPS to screen for PTSD under DSM-5 criteria, the PTSD Checklist for DSM-5 (PCL-5) [21].

The PCL-5 is a 20-item questionnaire to screen for PTSD symptoms and monitor patient progress. It is available in forms with and without questions related to trauma history, allowing the clinician to screen for a trauma history if required or to avoid questions if a trauma history has been established. The PCL -5 is available for download through the U.S. Department of Veterans Affairs and can be given to a patient to fill out in a waiting room. Completion of a PCL-5 usually requires between 5 and 10 minutes, and guidelines are available to establish a preliminary diagnosis of PTSD as well as to monitor for improvement following treatment, although both diagnosis and clinical progress should be confirmed by a clinician.

PTSD Prevalence

Estimates for prevalence of PTSD in the general civilian population range from 3% to 8.7%. Data from the National Comorbidity Study – Replication, an epidemiological study examining lifetime prevalence of various psychiatric disorders among the U.S. population – indicated that 3% of study participants met the criteria for PTSD during the past year [22], whereas 8.7% of study participants met the criteria for PTSD during their lifetime [23].

Estimates of PTSD in service member populations also vary. Over a decade ago, estimates of PTSD in service members predeployment were close to that of the civilian population (5%) [24]. During the first decade of the war, post deployment, early epidemiological studies indicated approximately 9–12% of OIF and 5–6% of OEF meeting diagnostic criteria for PTSD, including data from the Millennium Cohort Study, a large-sample study of deployed combat veterans [24–26].

More recently, Breslau [27] noted the prevalence of PTSD in nontreatment-seeking veterans of OIF/OEF has ranged from 5% to 20%, with PTSD positively associated with level of combat exposure [28]. Another recently published long-term prospective study by Vasterling and colleagues [29] found 24.7% of participants (n = 598) met case definition for PTSD 7.9 years after an Iraq deployment based upon clinician administered diagnostic interview.

A large epidemiological surveillance study by Brundage and colleagues [2] of all active duty service members deployed to Afghanistan or Iraq as well as Korea or Japan between 2003 and 2013 found the incidence of PTSD within 3 years after returning from war-zone service was 4.85 per 100 deployers. Of note, certain subgroups of deployers had a notably higher cumulative incidence rate of PTSD: healthcare occupations (8.52 per 100 deployers); combat-specific occupations (5.62 per 100 deployers); and those in the Army (6.76 per 100 deployers). Upon further analysis, Brundage et al. [2] found that up until 2007, war-zone service accounted for approximately four out of five postdeployment PTSD diagnoses. Beginning in 2007, the percentage of postdeployment PTSD diagnoses attributable to war-zone service began to shrink; by 2013, less than half of all postdeployment PTSD diagnoses were attributable to service in a war zone.

The Relationship Between PTSD and TBI

Historically, there had been a debate as to whether a person who has experienced a brain injury because of a traumatic event could go on to develop PTSD [8, 30]. This now antiquated thinking relied on the hypothesis that PTSD symptoms are a fear-conditioned memory of the traumatic event. Consequently, if a person sustains a head injury that results in impaired consciousness, the ability to encode memories would be disrupted, and, therefore, the person would be incapable of forming a fear-conditioned memory [31].

Today, the evidence is clear: PTSD after TBI can and does co-occur in both civilian and military populations. Bryant and Harvey conducted a series of studies between 1998 and 2000 that demonstrated the co-occurrence of brain injury and PTSD in civilian populations [32–34]. In one study (n = 79), 22% of participants met the criteria for PTSD 2 years postinjury [34]. A 2005 study [35] examining the relationship between memory for the traumatic event and the later diagnosis of PTSD in a small population of patients who required hospitalization for observation after a mTBI (n = 120) found that those patients who sustained an mTBI and who had a memory of the traumatic event were at a greater than two-fold risk for developing PTSD. In another study of OIF/OEF veterans (n = 12,605), Iverson and coauthors [36] found PTSD to be the most common psychiatric condition among veterans who had sustained a TBI.

The reported prevalence rates of comorbid PTSD and TBI in both the civilian and military population vary widely. In a systematic review of multiple studies examining military and veteran populations, Carlson and coauthors [37] found 10–40% of individuals with a confirmed or suspected history of a TBI had a diagnosis of PTSD. More recently, Bahraini and colleagues [8] examined civilian and military studies examining prevalence of comorbid TBI and PTSD. A review of studies examining the frequency of PTSD across levels of TBI severity in civilian populations found estimates of PTSD among those populations with mTBI range from 12% to 30%. In a similar analysis of 18 studies examining the prevalence of comorbid PTSD in the population with TBI in service member populations, the prevalence rate ranged from 12% to 89%. Of note, the authors highlight the wide disparity in study design, including choice of

clinician-administered diagnostic interviews in the civilian studies and the use of self-report checklists in the military studies. The use of the checklists may be problematic, as not all those that meet criteria using a checklist will meet full diagnostic criteria for PTSD.

While the exact reason is not entirely known, evidence is now clear that TBI is a known risk factor for the development of PTSD in both civilian and military populations [38–41]. In one large study (n = 13,201) of U.S. military Veterans, those with TBI were three times more likely to have PTSD [42]. More recently, Warren and colleagues [40], in a study of a civilian population (n = 494), found individuals with who sustained an mTBI at the time of an injury are at increased risk of developing PTSD.

Disentanglement of PTSD and mTBI Is Challenging

Given the lack of objective markers for mTBI and PTSD as well as the overlapping symptoms, the disentanglement of PTSD and mTBI can be challenging [8, 39]. Diagnosis cannot always be made by a simple review of symptoms. There is considerable overlap in the clinical presentation of PTSD and mTBI, including sleep problems, neurocognitive impairment, irritability, and other comorbid conditions, to include depression, substance use disorders, pain, and somatic disorders [43]. Furthermore, cognitive impairment, most often associated with a history of mTBI, is also common in PTSD, both in subjective patient report and on formal neuropsychological testing. Neuropsychological testing consistently demonstrates changes in sustained attention, working memory, processing speed, and verbal learning and memory correlated to PTSD symptom severity [44, 45]. A study of U.S. Army veterans who served in Vietnam (n = 4462) found that veterans who met criteria for postconcussive syndrome were more likely to be diagnosed with PTSD (40%) than to have a history of mTBI (32%) [46]. This creates a challenge for practitioners attempting to develop an accurate diagnostic picture. Careful history is useful: cognitive changes from mTBI are at their worst in the period immediately after the injury, whereas cognitive changes from PTSD worsen with duration of illness [47], and some symptoms are specific to each disorder and can be useful diagnostically (Table 2).

Table 2 Symptoms of PTSD and mTBI

PTSD	PTSD & mTBI	mTBI
Flashbacks	Anxiety	Headaches
Avoidance	Difficulty concentrating	Dizziness
Hypervigilance	Irritability	Nausea and vomiting
Nightmares	Depression	Vision problems
Re-experiencing phenomenon	Fatigue	Sensitivity to light/noise
	Insomnia	

Data from: Stein and McAllister [78] and Kennedy et al. [43]

The two symptoms most consistently correlated with mTBI are headaches and dizziness. Several studies have demonstrated that individuals who had sustained an mTBI were more likely to endorse headaches, dizziness, light sensitivity, problems with vision, sleep, and cognition. However, after controlling for all variables (including psychiatric), only dizziness, sleep problems, and memory problems remained significantly correlated with mTBI [47, 48]. Hoge and colleagues [38], examining U.S. Army infantry soldiers after return from deployment (n = 2525), found soldiers with a history of mTBI were significantly more likely to endorse a high number of physical health symptoms. When adjusted for depression and PTSD, only headaches remained high correlated with a history of mTBI.

Regardless of the etiology of symptoms common to both conditions, there is considerable evidence that treatment of PTSD is beneficial to patients with comorbid conditions of mTBI and PTSD. The landmark study by Hoge and colleagues [38] was the first to conclude that PTSD is an important arbitrator of the relationship between mTBI and poor health outcomes. More recently, Zatzick and colleagues [49] found that the presence of PTSD in those that have experienced a brain injury is correlated with increased self-reporting of impairment in cognitive functioning.

In another study of combat-injured service members, Belanger and associates [50] found that patients with mTBI were more likely to endorse postconcussive complaints that those with moderate-to-severe TBI; these differences persisted even when controlling for demographic variables, including age, mechanism of injury, and time from injury. Controlling for PTSD severity, however, eliminated the differences in perceived disability, indicating that symptom complaints in the mTBI patients may be correlated with emotional distress rather than attributable to the brain injury. Similarly, a small 2013 study comparing OEF and OIF veterans with PTSD only (n = 56) and TBI and PTSD (n = 40) by Ragsdale and colleagues [51] found those with PTSD and TBI endorsed significantly more intense, but not more frequent, PTSD symptoms. Regardless of the source of disability, treatment for PTSD results in cognitive and functional improvement of patients with comorbid PTSD and mTBI [38, 52, 53].

PTSD Treatment in Patients with Mild TBI

Due to a lack of studies showing different responses to treatment in PTSD patients with TBI as opposed to those without, the current VA/DoD CPG for mTBI (2016) is clear in recommending assessment and specific treatment for PTSD in accordance with the existing guidelines. A recent DVBIC research review [54] concluded, "there is no evidence that standard PTSD treatments are less effective in patients with mTBI history."

General principles exist for pharmacology in patients with moderate and severe TBI, such as those McCallister [55] recommended: (1) take a comprehensive approach, considering psychosocial needs; (2) obtain diagnostic clarity, initiating one agent at a time; (3) begin with lower medication dosages due to possible increased sensitivity to side effects; and (4) consider longer treatment trials to determine efficacy. While these are useful principles, there is no evidence that should cause an experienced clinician to deviate from his/her treatment algorithm, and treatments for individuals with PTSD and mTBI history should be guided by specific symptoms, regardless of etiology.

Best practices for the treatment of PTSD remain in dispute [56]. Major guidelines are divided on the relative merits of psychopharmacology and behavioral therapy. The Veterans Health Administration (VHA), DoD, American Psychiatric Association, and International Society for Traumatic Stress Studies guidelines consider psychopharmacology and behavioral therapy to be equivalent first-line therapies, while the World Health Organization and the National Institute of Health and Care Excellence guidelines consider behavioral therapy to be first line and superior to pharmacology [57, 58]. Overall, there are a larger number of high-quality studies supporting the use of behavioral therapy compared to psychopharmacology. With few exceptions, medication trials are limited by small effect sizes and diminishing benefits past 12 weeks of treatment. Conversely, first-line behavioral therapies typically show large effect sizes and clinical improvements that are either sustained or increased over time [56].

For these reasons, behavioral therapy should be considered an indispensable component of PTSD treatment. Current guidelines and reviews universally recommend forms of cognitive behavioral therapy, either prolonged exposure therapy (PE) or cognitive processing therapy (CPT), as first-line treatment of PTSD. The efficacy of these treatments for PTSD has been established in several well-designed, well-controlled trials [56].

Conceptually, PE and other exposure-based treatments (Eye Movement Desensitization and Reprocessing (EMDR) or Accelerated Response Therapy (ART) view the core symptoms of PTSD as the re-experiencing of previous traumatic events and avoidance of associated situations, even if these situations are not themselves inherently dangerous. PE treatment involves exposing the patient in a stepwise fashion to the avoided stimuli through a combination of two central techniques: imaginal exposure, where the traumatic memory is discussed and imagined, and in vivo exposure, where the patient is exposed to a noninherently dangerous situation associated

with the trauma [59]. Although these techniques are highly effective, some patients are unable to tolerate exposure-based treatments with reported discontinuation rates up to 41% [60].

CPT focuses on correcting maladaptive cognitions about the causes and results of trauma rather than directly confronting intrusive recurrent symptoms. Although there is less focus on trauma exposure than in PE, a course of treatment involves journaling traumatic experiences [61, 62], and a meta-analysis of 42 studies of psychotherapy for PTSD found no difference in discontinuation rates between PE and Cognitive Behavioral Therapy (CBT) [63]. Both of these forms of therapy consistently show large effect sizes and sustained gains in the treatment of PTSD; however, head-to-head studies to determine which approach has greater efficacy have had mixed results [64]. Referring providers would be well served to choose a provider skilled in approved therapy and allowing patient preference and fit with the provider to guide treatment modality given the relative equivalency of the approaches.

Given that the first-line treatment for PTSD is psychotherapy and many mTBI patients report challenges with memory and concentration, it may be important to make accommodations based upon the patient's individual needs. Patients who have sustained an mTBI are still able to engage in psychotherapy to address symptoms of PTSD. There are many ways in which both the structure and the therapeutic environment may be modified to accommodate the needs of patients with cognitive impairments (Table 3) [65].

Something as simple as reducing the length of the psychotherapy session or allowing for the use of written notes may make psychotherapy more palatable for patients with a history of mTBI.

The majority of guidelines recommend classes of medications, particularly selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs) for the treatment of PTSD; however, the evidence does not support this approach. While SSRIs are often thought of as a homogeneous collection of medications even by experienced psychiatrists, these medications vary widely in their actions on neurotransmitters other than serotonin and are neurochemically distinct, and the strength of evidence supporting their use for PTSD varies significantly. Only paroxetine (Paxil®, GlaxoSmithKline, Brentford, UK) and sertraline (Zoloft®, Pfizer, New York, NY, USA) have a Food and Drug Administration (FDA) indication for PTSD. Fluoxetine (Prozac®, Eli Lilly, Indianapolis, IN, USA), an SSRI, and venlafaxine (Effexor®, Pfizer, New York, NY, USA), an SNRI, also have studies supporting their efficacy. These studies are universally limited by small effect sizes, with the exceptions of venlafaxine and sertraline. Venlafaxine achieves large effect sizes in trials with duration less than 12 weeks, but its effect size is significantly diminished in longer studies as early as at 16 weeks [56]. Conversely, sertraline is less effective than venlafaxine, paroxetine, or fluoxetine in short-term trials, but is unique among pharmacological agents in demonstrating increasing efficacy over time [66]. In the absence of contraindications to their use, clinicians would be well served to use venlafaxine or sertraline in preference to other agents. All of these agents are generally well tolerated in patients, even those with a history of moderate or severe TBI.

Table 3 Structuring and accommodating the therapeutic environment with TBI patients

Ensuring environment has low stimulation	Promoting consistency, including a set structure
Minimizing distractions	Plan for longer duration of treatment
Having shorter, frequent therapy sessions	Find an individual's best time of day for sessions
Taking written notes	Using a session agenda to structure session
Use of visual aids	Allow for audio or video taping
Use role-playing	Use of nontechnical terms
Rating or scaling techniques to anchor changes in subjective experience	Allow for use of adaptive equipment
Use multimodal learning approaches	Summarize main points throughout session
End all sessions with a verbal summary of what is learned and next steps	

Adapted with permission of Oxford University Press from Kortte [65]

Classes of medications other than antidepressants have been studied for use in PTSD. However, currently, data do not support their use for the primary treatment of PTSD. In particular, antipsychotic medications and benzodiazepines, often used off-label for treatment of anxiety or insomnia, are contraindicated according to most major guidelines based upon lack of efficacy and evidence of significant health risks, including violence, worsening of clinical symptoms, cognitive decline, and overall mortality [67]. In patients with comorbid TBI, with their increased vulnerability to cognitive side effects and dystonic side effects, it is strongly recommended that these medications be avoided. Prescribers looking for medications for nightmares would do better to consider prazosin, although its efficacy for the primary treatment of PTSD is disputed [3, 56, 57, 68].

Interventional treatments (stellate ganglion block, repetitive transcranial magnetic stimulation, magnetic resonance therapy, hyperbaric oxygen therapy) are often of great interest to patients who are unable to tolerate exposure-based behavioral treatment or pharmacological interventions. Patients and advocates for these treatments will often cite studies in support of their efficacy. Universally, these studies are limited by lack of adequate controls [69, 70], small sample size [71, 72], lack of a gold-standard outcome metric [73], or all three [74, 75]. If the same standards of evidence used by the Institute of Medicine in 2008 or more recent meta-analyses [56, 68] are applied to these studies, there are only a series of small studies looking at rTMS [71, 72] that would meet criteria to influence clinical care, and these studies are inconsistent in their treatment protocol and vary in their findings. As a result, there is insufficient evidence to recommend any interventional treatment for first-line therapy, and they are not recommended as first- or second-line treatment by any major guideline.

A final point about the treatment of comorbid patients: Given the challenging nature and interaction of comorbid mTBI and PTSD, a carefully coordinated multidisciplinary approach to treatment is essential. Rehabilitation and treatment will be most effective when healthcare and social-care practitioners work as a coordinated, interdisciplinary team toward a common set of goals [76]. Polypharmacy is a significant problem in patients with TBI, and patients with comorbid mental health diagnoses are at an elevated risk. A study of 25,546 Iraq and Afghanistan Veterans found that 8.4% of TBI patients with comorbid PTSD and 23.2% of TBI patients with PTSD and depression were taking five or more medications with CNS effects. Even controlling for these diagnoses, polypharmacy in this population was associated with drug overdose and suicidal behavior [77]. Individual practitioners working in silos may lead to less than ideal outcomes, including unintentional drug-to-drug interaction, overuse of medication, and/or the unnecessary prescribing of medication that may contribute to cognitive impairment or mood lability.

Summary and Recommendations

The complex interaction between mTBI and PTSD in the military and veteran population is only beginning to be fully understood. Patients with TBI and PTSD can present clinically with similar symptoms, and both can display similar deficits on neuropsychological testing. In addition, these conditions have a compounding effect on each other in terms of disability. Treating PTSD has been found to be an effective means of decreasing disability in patients with residual cognitive symptoms from TBI of all severities [49]. Thus, clinicians treating either population should become familiar with and follow the recommendations for screening and treating both mTBI and PTSD. Fortunately, first-line treatment for PTSD includes exposure-based and cognitive behavioral therapies, which allow patients, who may be prone to polypharmacy, to be treated without medications. In cases where medications are indicated, there are a very limited number of medications with good evidence supporting their use for the treatment of PTSD, all of which are usually well-tolerated.

A significant portion of the recommendations made on the treatment of comorbid PTSD and TBI stems from a lack of data directly studying comorbid patients. There is a paucity of high-quality studies looking at treatments for

PTSD, particularly pharmacological and interventional studies. In particular, given the high number of patients with both diagnosis and the demonstrated efficacy of PTSD treatment in improving clinical outcomes, more studies are clearly needed that directly look at the efficacy of behavioral therapies and medications in this group. While behavioral therapies have outstanding efficacy and have been manualized to allow interested treaters to quickly learn evidence-based treatments, in situations where behavioral treatments are not an option due either to a lack of qualified treaters or a patient's inability to tolerate exposure treatments, more effective psychopharmacology or therapeutic interventions would be clinically invaluable. Thus, more high-quality studies are needed in this area to guide clinicians seeking to treat patients with comorbid PTSD.

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Behavioral and Psychiatric Comorbidities of TBI

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Introduction

An estimated 1.7 million Americans sustain a traumatic brain injury (TBI) each year [1], and over 5.3 million (2% of the United States [US] population) are currently living with a disability from TBI that requires assistance in activities of daily living [2]. The incidence of TBI, as measured by combined emergency department (ED) visits, hospitalizations, and deaths, has steadily risen from 521 per 100,000 in 2001 to 824 per 100,000 in 2010 [3]. Men are 1.5 times more likely to sustain a TBI than women, and military activities increase the risk of TBI [4]. Approximately 40.5% of TBIs are caused by falls, 14.3% by motor vehicle accidents, 15.5% by being struck by something or striking one's head against something, and 10.7% by assaults [3]. Among military personnel serving in a warzone, explosive blasts are the leading cause of TBI [5]. TBI is associated with a variety of subsequent neurological disorders, including epilepsy,

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Alzheimer's disease, and Parkinson's disease [6]. TBI has also been associated with a number of psychiatric and behavioral effects, including the development of mood and anxiety disorders, psychosis, aggressive behavior, and posttraumatic stress disorder (PTSD).

TBI Psychiatric Comorbidities

There are numerous and varied health and functional consequences of TBI, among the most challenging both to manage, but also to establish the precise link to TBI, are psychiatric problems. Reports of a potential relationship to TBI include disorders of mood, difficulties with anxiety, posttraumatic stress disorder, and behavioral disturbances. Differentiating diagnoses between various issues following TBI is complicated [7], as psychiatric symptoms following TBI, such as irritability and anger, are common to PTSD, depression, aggression, and some neuroanatomical lesions. In addition, substantial comorbidity may occur [8]; for example, Hibbard and associates [9] found that 44% of their sample with TBI reported two or more Axis I disorders on an average of 8 years following injury. Among 1560 adults who completed telephone interviews 1 year following TBI, approximately 40% reported clinically significant symptoms of mood or anxiety disorders [10].

Studies have found that premorbid psychiatric disorders, such as alcohol abuse, anxiety, and depression, increase the risk of postinjury depression or anxiety [7, 9–11]. Although it is unclear what proportion of individuals with TBI have psychiatric disorders prior to their injury, in general, 6.7% of individuals over the age of 18 in the USA experience major depression, and 18% experience an anxiety disorder each year [12].

Research suggests that the development of psychiatric issues following TBI may represent the developmental concept of *equifinality*, in which the same outcome (e.g., depression) may result from disparate causes and circumstances, such as premorbid dysfunction, poor psychosocial functioning after TBI, or nature and anatomic location of TBI.

Mood Disorders

Incidence rates of mood disorders following TBI vary. Prevalence estimates are 6–77% [10]; however, most experts approximate that post-TBI depression is evident in 25–50% of patients within the first year post injury and in 26–64% across the lifespan [9, 13–15]. This wide range in prevalence estimates is believed to result from a variety of methodological factors, including variation across studies in sample characteristics, severity and definition of TBI and depression, and assessment instrument [10]. The problem is further complicated by an overlap in symptoms between TBI, depression, and anxiety disorders (e.g., sleep disturbance, concentration difficulties).

Studies examining risk factors for depression after TBI have yielded mixed results (for discussion, see [11, 16, 17]); for example, some have found that older age [18] and female gender [19] significantly predict postinjury depression, whereas others have reported that these were not significant predictors [20–23]. Depression following TBI has been associated with poorer cognitive functioning [24, 25] and poorer psychosocial functioning [22, 26] than reported by those without depression. It has also been associated with a failure to recover as expected following TBI [20].

Factors that likely influence the risk of depression following TBI include genetic, demographic, developmental, and psychosocial elements [27]. That said, the exact etiology of these symptoms remains unclear; negative outcomes, such as poor psychosocial functioning, have been hypothesized to be both the cause [28] and consequence [26] of depression. Early psychosocial adversity (e.g., abuse), life stress, and limited social support are well-recognized risk factors for the development of psychiatric illness. These factors have not been extensively studied among TBI populations. However, preliminary research suggests that personal history of mood and anxiety disorders as well as previous poor social functioning are associated with the occurrence of major depression after TBI [7, 29]. Similarly, Fann and colleagues observed that the risk of psychiatric illness is highest shortly after injury in persons with no previous psychiatric history,

was unrelated to the severity of TBI, and appeared to increase in subsequent years in persons with premorbid psychiatric disorders [30].

It is also possible that for some individuals, depression following TBI may reflect an organic etiology [18] associated with the neurological issues associated with TBI; for example, lesions in the regions such as the left dorsofrontal cortex, left basal ganglia, or right posterior hemisphere have distinguished depressed and nondepressed patients with TBI [17]. Taken together, this research suggests that the development of psychiatric issues following TBI may represent the developmental concept of *equifinality*, in which the same outcome (e.g., depression) may result from disparate causes and circumstances, such as premorbid dysfunction, poor psychosocial functioning after TBI, or nature and anatomic location of TBI.

Anxiety Disorders

Anxiety disorders (other than posttraumatic stress disorder [PTSD], see below) are relatively common in patients who have sustained a TBI, but estimated prevalence rates vary greatly. Some estimates suggest prevalence of anxiety after TBI is as high as 70%; however, a meta-analytic review by Epstein and Ursano [31] demonstrated prevalence of anxiety disorders being lower – 29% across all severities of TBI. Although some are much more prevalent than others, virtually all types of anxiety disorders have been documented following TBI. Research indicates that the rates of anxiety disorders among patients with TBI are 3–28% for Generalized Anxiety Disorder (GAD), 4–17% for Panic Disorder, 1–10% for phobic disorders, 2–15% for Obsessive-Compulsive Disorder (OCD), and 3–27% for PTSD [15, 32]. Such acquired anxiety disorders are presently coded in the Diagnostic and Statistical Manual-5 (DSM-5) as "Anxiety Disorder Due to Another Medical Condition" [33]. In general, the most common post-TBI anxiety symptoms include free-floating anxiety, fearfulness, intense worry, generalized uneasiness, social withdrawal, interpersonal sensitivity, and anxiety dreams [34]. Increased activity of the aminergic system and decreased activity of the GABA inhibitory network is the proposed mechanism for the clinical manifestation of anxiety [35]. Right-hemispheric lesions are more often associated with anxiety disorder than left-sided lesions [36].

Posttraumatic Stress Disorder

Exposure to trauma, such as the potentially life-threatening events associated with TBI (e.g., motor vehicle accidents and combat), places individuals at risk for various psychiatric disorders, most notably PTSD. As defined by the American Psychiatric Association, PTSD is a constellation of symptoms, including re-experiencing the event, avoidance of reminders of the event, negative alterations in cognitions and emotions, and chronic hyperarousal that persist for 3 months or more after exposure to a trauma [33]. Given the increased risk of both trauma and TBI in combat, the recent wars in Iraq and Afghanistan have highlighted the complications associated with identifying TBI in the context of PTSD and vice versa. In a sample of 100 soldiers with similar combat experience, 16.7% of those who incurred a bodily injury during combat met the criteria for PTSD after deployment, while only 2.5% of those without injury were diagnosed with PTSD [37]. The association between injury and later development of PTSD appears to be even greater in the case of mild TBI (mTBI, or concussion) relative to other bodily injuries. Hoge and associates [38] noted a strong association between combat-related mTBI and screening positive for PTSD. In a stratified sample of soldiers who reported a history of no injury, nonbrain injury, mTBI with altered mental status, and mTBI with loss of consciousness, the rate of positive postdeployment PTSD questionnaire screenings rose steadily from 9.1% in the nonbrain injury group to 43.9% in the mTBI with loss of consciousness group. What remains unclear is if this relation between PTSD and history of mTBI would be changed if more stringent diagnostic standards for PTSD and mTBI (i.e., clinician-confirmed diagnosis) were employed. This frequent occurrence of PTSD symptomatology after mTBI is not unique to military populations. Estimated rates of PTSD

following mTBI have ranged from 17% to 33% in civilians with TBI [39–41], a rate of PTSD considerably higher than 7.8% lifetime prevalence rate noted in the civilian population [42].

The topic of PTSD following mTBI has caused considerable controversy for two reasons. First, the development of PTSD is assumed to stem from intense psychological trauma wherein the perceived potential for loss of life, physical injury, or sexual assault is present. From this perceived threat at the time of the traumatic event, the individual subsequently "cannot forget" the trauma as evidenced through re-experiencing the trauma, avoiding situations, thoughts, and feelings that serve as reminders of the trauma, subsequent changes in one's thinking and emotions, and hypervigilance toward perceived threats. It has been questioned whether this psychological response to a traumatic event can occur in the context of a TBI associated with loss of memory for the event.

An early study on this topic appeared to validate the logical conclusion that mTBI should serve as a protective factor against later PTSD [43]. Of the 70 patients with either PTSD or a history of mTBI included in this study, none of the patients with a history of TBI reported any re-experiencing symptoms, consistent with the expectation that an amnestic state associated with an mTBI would preclude later recall of the event. Of note, the majority of patients in this study either reported loss of consciousness or amnesia for the event (i.e., 85.7% reported a positive loss of consciousness, and 96.4% reported amnesia for the event), suggesting that this sample may have included a disproportionate number of patients with somewhat more significant mTBIs. A more recent study exploring the association between memory for the traumatic event and later development of PTSD suggested that those patients with mTBI without amnesia for the event were at increased risk of developing PTSD relative to those patients without memory for the event [44]. The representativeness of the 120 patients in this study has also been called into question, however, since all the patients required hospitalization for observation.

Other studies, however, have failed to support the hypothesis that amnesia for the traumatic event surrounding the mTBI reduces the likelihood of developing PTSD. Studies of civilians indicated that a history of TBI with loss of consciousness was a risk factor for development of PTSD [45, 46]. King [47] offered three explanations for the paradoxical appearance of PTSD (especially re-experiencing symptoms) following a TBI with apparent loss of consciousness or posttraumatic amnesia proximal to the traumatic event. First, it is possible that islands of memory persist during the period of apparent amnesia. Second, an implicit fear response may still be evoked when a person is exposed to stimuli reminiscent of the traumatic event even if there was a clear loss of consciousness. Lastly, individuals without memory for the traumatic event may develop imagined or reconstructed memories based on information provided by others.

Another problem related to the comorbidity of TBI and PTSD concerns the considerable overlap in PTSD and postconcussion symptoms. Sleep disturbance, irritability, memory and concentration difficulties, reduced speed of processing, depression, fatigue, headaches, and nausea are common to both disorders [47]. As might be expected, the presence of PTSD following mTBI is associated with increased postconcussion symptoms reported, and PTSD symptoms are correlated with postconcussion symptoms. In a sample of 105 motor vehicle collision survivors with and without mTBI, the frequency of reported postconcussion symptoms was greatest in individuals who sustained an mTBI and had been diagnosed with PTSD, and overall report of PTSD symptoms was significantly correlated with the report of postconcussion symptoms [48]. Longitudinal studies of PTSD and postconcussion symptoms demonstrate that PTSD accounts for the lingering postconcussion symptoms rather than the original head injury [49–51].

In the context of combat-related mTBI, the controversy of mTBI as a risk factor for PTSD is different. Unlike the civilian population where a single event is theorized to precipitate both the mTBI and subsequent PTSD, the traumatic event that is associated with a combat-related mTBI often represents perhaps one in a series of psychologically traumatic events and exposure to

heighted combat intensity taking place over several months [38]. In this context, a diagnosis of mTBI simply serves as a proxy indicating a likely history of exposure to repeated, traumatic events, any of which could have contributed to the later development of PTSD. Although further research is needed to better delineate the interplay between these two disorders, it could be hypothesized that an mTBI occurring in the context of acute stress disorder or PTSD has the potential to worsen the psychiatric disorder through a temporary reduction in cognitive resources used to process the ongoing trauma. Conversely, chronic stress associated with the presence of acute stress disorder or PTSD could impede or otherwise alter the trajectory of the course of spontaneous recovery of cognitive functioning following mTBI.

Fortunately, comorbid mTBI and PTSD are generally not associated with greater impairment than either diagnosis alone. There are some exeptions, to include comornid mTBI and PTSD being related to increased medical costs, PTSD symptom severity [52, 53], and increased pain intensity levels [54]. However, the majority of functional outcomes do not appear to be negatively affected by the comorbidity of the disorders. For example, comorbid mTBI did not elevate the risk of suicide [53], negative physical health outcomes (with the exception of headaches; [38]), arrest rates [55], impaired psychosocial functioning [56], or alcohol use disorder [57] above PTSD alone. Similarly, PTSD did not lead to impairments in cognitive ability above mTBI [58]. Psychiatric symptoms and coping abilities may be more important in predicting mTBI complications than the severity of the head injury. A civilian study conducted in the Netherlands demonstrated that patients who experienced an mTBI and reported many postconcussive complaints 2 weeks after the injury were more likely to be female, endorse psychiatric symptoms (anxiety, depression, and/or PTSD), have fewer active coping mechanisms, and have more passive coping tendencies than patients who reported few or no symptoms. The severity of the head injury did not predict complaints [59].

Psychotic Symptoms

Although a relatively rare complication, psychotic symptoms may emerge secondary to TBI. Psychotic symptoms following TBI can manifest as frank delusions, hallucinations, and disordered thinking. They may also be associated with symptoms of agitation, ideas of reference, grimacing, inappropriate laughing, and impulsive aggressiveness (discussed below; [60, 61]). The psychotic features may be acute or chronic, transient or persistent, and may or may not be associated with mood disturbances [62]. Nevertheless, the association between psychosis and TBI remains quite controversial. Psychotic syndromes occur more frequently in individuals who have had a TBI than in the general population. A review by Davison and Bagley [63] revealed that 0.7–9.8% of patients with TBI develop schizophrenia-like psychosis. The majority of those patients did not have a family history of schizophrenia. Other studies have shown that the incidence of head injury predating psychotic symptoms in a population of patients with schizophrenia is about 15% [64]. David and Prince [65] reviewed the literature to identify a causal role of TBI in psychosis and concluded that the evidence for such an association does not exist. They suggest that any association may be the result of reverse causality. It is clear that large-scale epidemiological studies are needed to determine if TBI can be considered to be causally implicated as a risk factor for schizophrenia-like syndromes [66].

Suicide

Just as depression and other psychiatric conditions are associated with an increased risk of suicide [67, 68], a history of TBI must also be considered when assessing suicide risk. In their review of the relation between TBI and suicidality, Simpson and Tate [69] concluded that those recovering from TBI have a three- to four-fold increased risk of committing suicide relative to the general population, and that this increase appears to remain constant at least through the first 15 years post injury. A recent Danish population-based study including nearly 150,000

subjects examined the relationship between TBI severity and suicide risk [70]. While those with severe TBI, as defined by the presence of cerebral contusions or intracranial hemorrhages, demonstrated the highest risk of suicide (i.e., 4.1 times increased risk) relative to the general population, those classified with a concussion still demonstrated an increased risk of suicide (i.e., three times increased risk). It has been suggested, however, that the increased rates of suicide for mTBI are likely related to postinjury and/or concomitant psychosocial factors, whereas suicidality following severe TBI is likely related to the injury and subsequent sequelae [69].

Given that the vast majority of combat-related TBIs from the current wars in Iraq and Afghanistan are classified as mild [68], the relation between TBI severity and suicidality must be carefully considered in order to fully appreciate the potential implications for health management of returning military personnel and veterans. Although causal attribution cannot be drawn from correlational studies, the possibility that such an association exists between combat-related concussion and suicide has extremely important implications for mental health screening and suicide prevention efforts given the relatively high incidence of history of concussion in returning military personnel (estimated to be between 5% and 20% of service members in deployed units [68]). Future attempts to further explicate the complex relation between concussion and suicide must take into account the various shared risk factors between TBI and suicidality (e.g., young age, male gender, substance abuse, aggression/impulsivity) to determine the extent to which concussion uniquely contributes to suicide risk [71].

TBI Behavioral Comorbidities

Aggressive Behavior

Aggressive behavior following TBI complicates rehabilitation [72], is a concern for caregivers [73], and has been associated with lower psychosocial functioning 10 years following injury [26]. The reports of prevalence and frequency of aggression following TBI differs based on definition/severity of TBI, definition and assessment of aggression, reporting period, reporter (self, caregiver, staff), sample, and timing of assessment. Aggression following TBI may be expressed as agitation [72, 74], intimate partner violence [75, 76], suicide attempts [77], sexual violence or sexual disinhibition [78, 79], verbal aggression [80], or physical aggression [81]. As in the general population, verbal aggression typically is more frequent than physical aggression [79, 80]. The frequency of aggression following TBI has ranged from 11% to 96% based on the form of violence and the assessment instrument used (as reported in [82]). Using the Overt Aggressive Scale (OAS, [83]), Tateno and associates [82] found that 33.7% of patients with TBI compared to 11.5% of patients without TBI reported aggressive acts in the 6 months following their injury. Using the Overt Aggression Scale—Modified for Neurorehabilitation (OAS-MNR, [84]), Alderman [81] reported 5548 episodes of aggression perpetrated by 108 patients with severe neurological damage over 14 days on an inpatient unit. The authors noted that the episodes were triggered by staff prompts or erupted with no apparent provocation. Using the OAS, Baguley and associates [85] reported that rates of aggression among patients with moderate-to-severe TBI fluctuated over the 5 years following injury, but that at any given time, approximately 25% of patients with TBI were expressing "severe" aggression. Similarly, among individuals who survived severe TBI and were followed for 3 years, 55% of those whose injury occurred *more than* 18 months ago had verbal or physical aggression as reported by family members compared to 13% of those whose injury occurred *less than* 18 months ago [73]. Thus, frequency and severity of behavioral problems (aggression and other problems) were not related to the time since injury or the severity of head injury, respectively. Using the Buss Perry Aggression Scale (BPAQ, [86]), Dyer and associates [80] compared a sample of participants with TBI to those with spinal cord injury (SCI) and those without injury on measures of anger, aggression, and impulsivity

10 years following injury. Participants with TBI (severity not specified) reported more impulsivity, anger, and verbal aggression than those with SCI. When caregiver's reports were used, participants with TBI were also rated as more verbally aggressive than those with SCI. TBI has also been associated with anger and aggression among forensic samples. Slaughter and coauthors [87] randomly selected 69 inmates of a county jail of whom 87% reported a lifetime history of TBI (67% mild, 33% moderate/severe) and 36% reported a TBI (80% mild, 20% moderate/severe TBI) in the past year. Based on the Brief Anger and Aggression Questionnaire (BAAQ, [88]), more extreme anger and aggression were reported by those with TBI than those without. Similarly, using the index offense of record, Brewer-Smyth and coauthors [89] found that women incarcerated for a violent crime had more TBIs with loss of consciousness in their lifetimes than those incarcerated for a nonviolent crime; however, only one participant convicted of a violent crime reported severe brain injury.

TBI and potential links to aggression have been examined among military samples; Vietnam veterans with TBI from penetrating brain wounds reported more aggression and violence than those without TBI [90]. At the time this chapter was written, the association between TBI and aggression had not been examined systematically among military personnel serving in Operation Enduring Freedom and Operation Iraqi Freedom, but the consequences of TBI are a concern, given the proliferation of improvised explosive devices (IEDs) used in these conflicts. Among the personnel serving in Iraq, it is estimated that approximately 11% meet the criteria for mTBI through surveys [91]. In a similar vein, among a sample of 2525 Army infantry soldiers serving in Iraq, Hoge and coauthors [38] reported that 4.9% reported loss of consciousness and 10.3% reported altered mental status. Although survey data provide clues about the possible scope of the problem, survey reports of TBI symptoms and criteria are not necessarily confirmed by a clinical assessment and, therefore, may not accurately estimate prevalence by overestimating it.

Aggression following TBI often co-occurs with other postinjury psychiatric and psychosocial issues, such as anger [80], hostility [77], impulsivity [80], depression [85], PTSD [92], and substance abuse [26]. Though premorbid factors, such as alcohol use, may influence the presence (TBI versus no TBI, [77]) and etiology (i.e., whether due to violent or nonviolent causes, [93]) of TBI, these factors seem to be less predictive of postinjury aggression than the other postinjury psychosocial issues. For example, in a 5-year follow-up study, age and depressive symptoms, as rated with the Beck Depression Inventory [94], were the only factors that predicted aggression at 6-, 24-, and 60-month follow-up [85].

Impulsivity

Impulsivity and substance use, specifically alcohol use, have been associated with a variety of violent acts and are thought to be associated via shared biological substrates or altered social information processing [95, 96]. The comorbidity may also be an artifact of the diagnostic criteria for psychiatric disorders, which may include irritability, anger, impulsivity, and aggression [97]. Given these similarities, it is unclear what distinguishes TBI aggression from that observed among noninjured individuals and consequently what novel aspects for TBI-aggression treatment would need to be considered. Because TBI involves lesions to the brain, usually in the frontal lobes, it is possible that specific executive function deficits experienced by individuals with TBI and aggression may provide clues to understanding the phenomenology and treatment of this behavioral problem. Group differences on executive deficits have been examined among individuals with TBI based on the etiology of their injury (violent versus nonviolent), with results suggesting that premorbid factors, and not the nature of injury, influence the outcome following TBI [93, 98]. In a study of sex differences in executive functions among individuals with TBI, women outperformed men on neuropsychological assessments, but demographics (e.g., gender, minority status, education), premorbid history (e.g., history of illicit drug use), and factors related

to the injury (e.g., cause of injury, length of coma) were most predictive of neuropsychological functioning among men and women [99]. When comparing men with and without TBI who were receiving court-ordered treatment for intimate partner violence, men with TBI had poorer executive functioning and lower postinjury IQ than the non-TBI batterers [76]. Underscoring the importance of considering premorbid differences, these studies do not yet definitively establish how executive functions may be associated with aggression post TBI.

Orbitofrontal regions have been associated with alterations in behavior, including impulse control, since reports of the prototypical patient with frontal injury, Phineas Gage [100, 101]. Studies specifically of impulsive aggression among individuals with TBI suggest associations with lesions of the ventromedial prefrontal cortex [102] using neuropsychological testing sensitive to this region (e.g., Revised Strategy Application Test). One difficulty in generalizing subtypes of aggression and their relationship to neuroanatomical underpinnings from the extensive literature on aggression in TBI is that impulsivity and impulsive aggression are often equated, whereas, at least in highly impulsive individuals with antisocial behavior, the degree of impulsivity does not itself distinguish those with predatory versus impulsive aggression, but the existence of language impairments and parietal electrophysiological processing differences did distinguish them [103, 104]. This research suggests that impulsivity alone is not sufficient to cause an individual to become impulsively aggressive, and it is likely that additional deficits that may be associated with TBI are important to this condition. Initial work in long-term survivors of severe TBI with impulsive aggression did not demonstrate these specific neuropsychological abnormalities, suggesting that there may be alternative pathways to impulsive aggression [105]. However, in this study, premorbid functioning was associated with impulsive aggression, suggesting that it may be difficult retrospectively to delineate the specific contribution of the TBI to the behaviors of interest.

Treatment of Behavioral Disorders Following TBI

Treatment of behavioral problems following TBI, including impulsive aggression, a hair-trigger response to a threat with a behavioral loss of control [106], has been recently reviewed by Warden and coauthors [107]. This and earlier reviews of therapy (e.g., [108]) demonstrate a paucity of large randomized trials that address behavioral outcomes. While there is little in the way of large randomized, long-term trials specifically in TBI patients to recommend most therapies, promising research implicates certain pharmacological approaches, such as beta-adrenergic-receptor-blocking agents. Other potential agents, in which most work has involved aggression in other conditions but with some support following TBI, include anticonvulsant agents such as carbamazepine and valproic acid [108]. Phenytoin shows a very specific benefit in reducing the severity and frequency of impulsive aggression acts [103, 104, 106], although this work was in patients with no evidence of past symptomatic TBI and with a normal EEG. It remains to be studied whether this work will translate to patients post TBI. As with all of these agents, a thorough understanding of their side effects is necessary to tailor individual assessments of risk and benefits.

Treatment recommendations of behavioral disorders in TBI patients generally involve targeting symptoms, such as attention, mood, and psychotic symptoms. Evidence on effectiveness in the treatment of other psychiatric disorders occurring in the TBI patients is similarly limited, but general treatment recommendations include agents shown to be beneficial in these conditions in non-TBI patients, including selective serotonin-reuptake inhibitors and anticonvulsants as well as nonpharmacological, behavioral therapies [107, 109]. There is currently great interest in the possibility of treatment of PTSD in combat veterans using the adrenergic agent, prazosin [110]. Benefit for nightmares was initially suggested, although a recently published randomized clinical trial failed to demonstrate medication efficacy [111].

There are several reviews addressing the efficacy of treatments for persistent postconcussion symptoms of mTBI (e.g., [112–114]), although there are few well-designed studies. Treatments following mTBI vary depending on factors, such as time since injury and the symptoms experienced following the event. In general, mTBI treatments can be viewed as falling into one or more of the following four categories: cognitive behavioral therapy, cognitive remediation, pharmacotherapy for symptom-based management, and education and support, depending upon the symptoms present. While the TBI symptoms may need to be monitored and treated, it is fortunate that psychotherapy for psychiatric disorders, such as PTSD, is effective for those with and without comorbid mTBI [115]. We present a basic treatment algorithm (Fig. 1) that describes mTBI interventions, both for symptom reduction and prevention of postconcussion symptoms, for military personnel and veterans at various time points postinjury. This model assumes the presence of unit and military medical personnel who are familiar enough with injury severity characteristics to assist in classifying a suspected mTBI (Fig. 1).

Individual- and population-based mTBI screening instruments, such as the Standardized Assessment of Concussion [116] upon which the more recent Military Acute Concussion Evaluation is based [117] and the Brief Traumatic Brain Injury Screen [4], have shown promise, although verification of the diagnosis through follow-up clinical interview is still necessary due to false-positive errors (e.g., [118, 119]. As described earlier in this chapter, consensus criteria for concussion/mTBI are available to improve diagnostic accuracy [120, 121]. Once the diagnosis has been verified and the specific symptoms have been detailed through clinical interview, symptom management and work restrictions should be considered, with the goals being to maximize functional recovery [122]. While these first two aspects of treatment are meant to reduce the immediate impact of mTBI, the third component of treatment is aimed at reducing the subsequent development of postconcussive symptoms. It is during this period of time shortly following mTBI that psycho-education has been determined to be the most effective for the purpose of reducing subsequent postconcussion symptoms [112]. However, it is important to note that in the World Health Organization (WHO) review of mTBI interventions, no treatments were found to provide clinically important effects on symptoms or disability, although there was some evidence to suggest that early education and limited support (e.g., information about common complaints and the likelihood for a good outcome) as to the effects of mTBI may reduce future symptom complaints [112]. This approach of intervening after exposure to a trauma in order to reduce the likelihood of future maladjustment has also met with success in the management of PTS symptoms in military personnel following combat deployment [123].

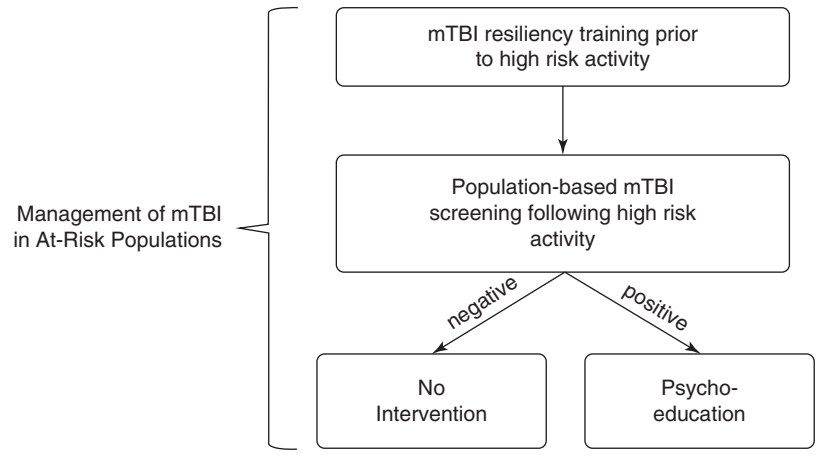

Fig. 1 Management of mTBI during acute recovery. The treatment algorithm for the management of mTBI during acute recovery is based on earlier work by Mittenberg et al. [123], Paniak et al. [126], and others who have demonstrated the effectiveness of brief interventions for reducing the severity of symptoms following mTBI

Based upon their research regarding misappraisal of symptoms in mTBI patients (see above), Mittenberg and coauthors [124] developed an effective, brief 1-hour educational intervention. The effectiveness of this intervention in decreasing later postconcussive symptoms was demonstrated in 58 consecutive mTBI hospital admissions (GCS $\geq$ 13, Galveston Orientation and Amnesia Test score >75, no significant extracranial injuries). Half of the patients were randomized into a treatment arm during which time they met with a therapist to discuss symptoms for approximately 1 hour and were provided with educational materials. The other patients received routine care and were provided with written discharge instructions that were verbally reviewed by a nurse. Six months after admission, mTBI patients in the treatment arm reported reduced symptom duration (33 days versus 51 days) and a lower number of postconcussive symptoms (1.6 symptoms versus 3.1) relative to the patients who received the standard of care [124, 125]. More recently, psychoeducation and support provided via telephone calls (four calls at 2, 4, 8, and 12 weeks postinjury) were also shown to be effective at reducing postconcussive symptoms 6 months post-mTBI relative to standard emergency room care (e.g., instruction handout) [126]. The relative benefit of the follow-up telephone calls is difficult to determine due to the design of the study, although the results of other mTBI intervention studies indicate that more than one treatment session may not have an added benefit [127, 128].

Diagnostic criteria have also been developed to identify those individuals who experience an abnormal persistence of postconcussion symptoms following mTBI. The International Classification of Diseases, Tenth Revision, criteria include a history of TBI and the presence of three or more of the following eight symptoms: headache, dizziness, fatigue, irritability, insomnia, concentration difficulty, memory difficulty, and intolerance of stress, emotion, or alcohol [129]. Boake and colleagues [130] noted that the prevalence of diagnosed postconcussion symptoms was higher 3 months post injury using the ICD-10 criteria (64%) relative to the DSM-IV-TR criteria (11%) in a sample of 178 adults with mild-to-moderate TBI, although both criteria showed poor specificity when tested with a control sample of 104 adults with extracranial injuries. The authors noted that the nonspecific ICD-10 PCS criteria likely contributed to the higher diagnostic rates using that classification scheme, while the lack of specificity demonstrated by both classification schemes was due to frequent endorsement of symptoms by patients without cranial injuries. While the DSM-IV-TR proposed criteria for the diagnosis of postconcussion disorder, the DSM-5 subsumes persisting postconcussion symptoms under the diagnosis of Mild Neurocognitive Disorder due to Traumatic Brain Injury. Injury severity in the DSM-5 framework is loosely based on traditional injury severity characteristics (e.g., LOC, PTA, GCS score), whereas any neurocognitive symptoms, to include postconcussion symptoms, temporally linked to the TBI and persisting beyond the acute postinjury period would be captured as a neurocognitive disorder (NCD). It should be noted that "acute postinjury" is not defined within the DSM-5. While the DSM-5 indicates the "severity of the TBI itself does not necessarily correspond to the severity of the resulting neurocognitive disorder," this is generally inconsistent with extant mTBI literature as well as an indication within the DSM-5 that "neurocognitive symptoms associated with mild TBI tend to resolve within days to weeks after the injury with complete resolution typical by 3 months." The DSM-5 does acknowledge that there are overlapping symptoms between neurocognitive disorder due to TBI and PTSD, including postconcussion symptoms, thus increasing the clinical challenge in considering the differential diagnosis.

For military personnel who subsequently develop postconcussion symptoms, the U.S. Department of Veterans Affairs and Department of Defense recommend a combination of both psychoeducation and symptom management (Fig. 2) [131]. The effectiveness of this treatment paradigm, especially the provision of psychoeducation to veterans who may be several years post injury, has yet to be determined. From a theoretical standpoint, it may be possible that

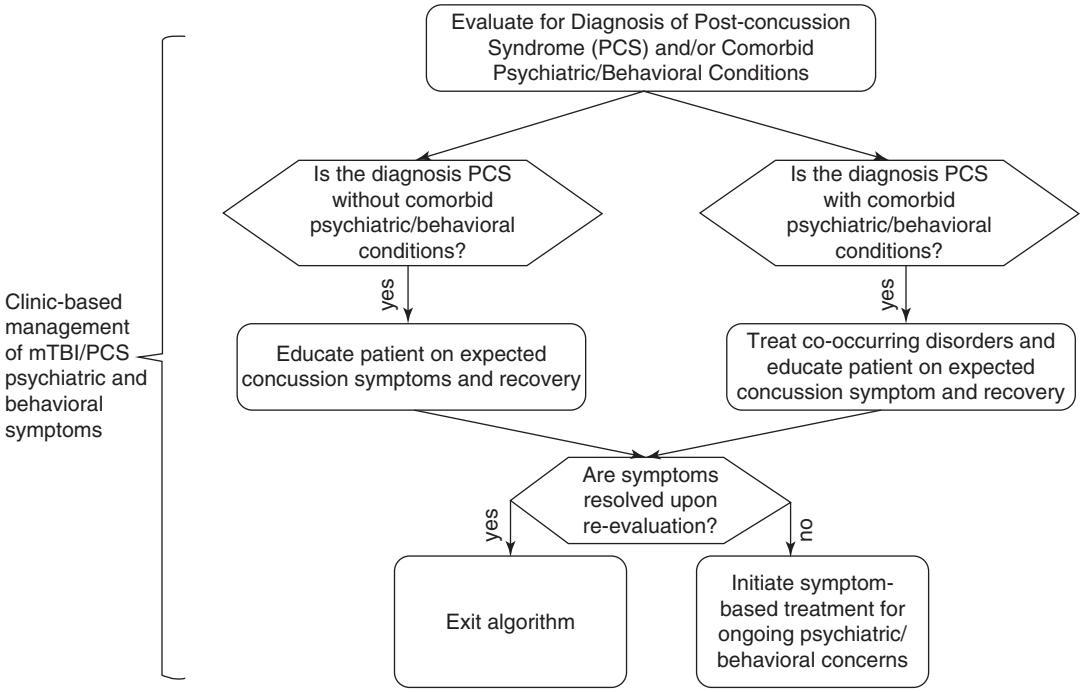

Fig. 2 Management of PCS. The treatment algorithm for the management of PCS is designed in part after the treatment recommendations offered by the U.S. Department of Veterans Affairs and Department of Defense [131]

allowing postconcussion symptoms to develop without early education allows patients to develop resistance to subsequent attempts at reducing postconcussion symptoms through education. That is, once erroneous expectations about consequences of mTBI are left unchecked for many months or years post injury, patients may be reluctant to consider other causes of their symptoms. There may be some benefit to early psychoeducational intervention for military personnel prior to deployment in that education at this level may provide resiliency in terms of subsequent development of postconcussion symptoms following mTBI. More recently, the U.S. Army implemented the Comprehensive Soldier Fitness (CSF) program, designed to increase the psychological resilience and reduce the incidence of maladaptive responses among U.S. Army soldiers [132]. While this training does not appear to directly address TBI and mTBI sequelae, it is possible that some benefit may be seen in terms of the shared PTSD-postconcussion symptoms as the CSF is multifaceted and, among other goals, works to both increase resilience to combat-related stress and also inform soldiers about the psychological consequences of combat exposure to include both PTSD and posttraumatic growth [133]. At present, there are no studies addressing the effectiveness of predeployment resiliency training to include the more recently implemented CSF. We believe, however, that such resiliency training is a natural extension of the literature and is meant to augment, rather than replace, psychoeducational interventions that should occur immediately after a service member sustains an mTBI.

Epidemiology and Classification of mTBI with a Focus on Symptoms

Approximately 70–90% of head injuries are classified as mild in nature [134, 135]. Incidence rates of mTBI in the civilian population, however, are widely considered to be underestimated, since approximately 25% of individuals suffering an mTBI do not seek medical attention [136]. As with moderate-to-severe TBI, the rate of mTBI is

greatest in males and young adults, and the most common mechanisms include motor vehicle accidents and falls [137]. Similar to the civilian population, the majority of military TBIs are mild. In fact, the incidence of mTBI in contemporary warfare may be on the rise due to the prevalent use of explosive munitions (i.e., IEDs and mines). In one study, 22.8% of soldiers returning from the Iraq War were noted to have a history of at least one mTBI during deployment, most of which were mild in nature [138]. It is estimated that by 2008, as many as 300,000 soldiers had suffered an mTBI in the wars in Iraq and Afghanistan [68], although this may be an inflated estimate based on the lack of validity of the diagnostic criteria used to derive the approximation [139]. These issues are important to address as the definitions and context affect our understanding of the psychological and psychiatric effects of TBI.

Characterization of the psychiatric comorbidities of mTBI is complicated by the lack of uniformity in the definition of mTBI [136]. The diagnosis of mTBI is based on the assessment of acute injury severity characteristics immediately following an injury to the head resulting from blunt trauma and/or acceleration or deceleration forces. Most contemporary mTBI classification schemes require a period of impaired consciousness (including loss of consciousness), memory dysfunction for a period of time surrounding the injury (i.e., retrograde or posttraumatic amnesia), or neurological or physiological dysfunction (e.g., seizures, lethargy, and vomiting) proximal to the time of injury. In order to create a clearer boundary between those with mild versus those with moderate-to-severe TBI, the American Congress of Rehabilitation Medicine (ACRM) consensus group suggested that those with mTBI experience a loss of consciousness of no greater than 30 minutes, experience a posttraumatic amnesia of no greater than 24 hours, and should have a Glasgow Coma Scale (GCS) score of 13 or greater within 30 minutes after their injury. The ACRM definition of mTBI has gained traction in the research and clinical community over the last 15 years and has been adapted by other health agencies [136]. Within the field of psychiatry and psychology, the DSM-5 modeled its set of TBI criteria on the ARCM definition described above. TBI and its neuropsychiatric sequelae are addressed principally within framework of the Neurocognitive Disorders.

Although general consensus has been reached regarding the diagnostic criteria for mTBI, several shortcomings of the diagnostic system have been identified. Without direct observation from trained bystanders or emergency medical technicians, there is no way to verify that the minimal criteria for mTBI were present at the time of the injury (i.e., brief period of altered mental status). Despite the apparent fallibility of relying on retrospective, self-reported changes in mental status to establish a history of mTBI, this is considered standard practice in diagnosing mTBI [140, 141] and has been recommended by the Centers for Disease Control in cases of nonmedically attended TBI [136]. Additionally, alcohol and recreational drugs present at the time of injury or therapeutic drugs administered in the immediate postinjury period can cause alterations in consciousness and perturbations in autobiographic memory, all of which can be mistaken for injury-related alterations in mental status [141].

Diagnosing a history of combat-related mTBI presents even greater challenges. First, a brief period of altered mental status may go unreported in the middle of life-threatening events like close proximity to a detonated IED, an event that has been exceedingly common during the Iraq and Afghanistan conflicts [138, 142]. Second, symptoms related to mTBI may be overlooked in the presence of other combat-related injuries that require immediate medical attention (e.g., traumatic amputations, lacerations, and burns). These first two diagnostic issues would result in an underidentification of a history of mTBI. Third, common diagnostic criteria with reasonable specificity in the civilian population, such as feeling dazed or confused, may result in insufficient levels of specificity when applied to injuries incurred during combat deployments. Conversely, a brief period of confusion or disorientation may represent a psychological reaction to an unexpected, highly stressful event rather than a mani-

festation of underlying brain injury. The third diagnostic issue would, thus, result in an overidentification of a history of mTBI.

Because of the definitional issues and difficulty of assessing for TBI criteria immediately postinjury, many studies evaluating the impact of mTBI have had widely different findings (e.g., [143, 144]). For example, many people do not seek treatment following mTBI as there is a likely perception that mTBI will have few meaningful consequences. This sharply contrasts with the established and adverse consequences that are associated with moderate-to-severe TBIs. For those patients that do seek emergent care, a GCS may be obtained, but this instrument is not suited to assess the more subtle cognitive changes that are likely to occur following an mTBI [145]. In both clinical and research settings, comprehensive neuropsychological evaluations in the period following mTBI are typically not undertaken, and even fewer evaluations are likely to occur at more distal time points. For this reason, comparatively less is known about the impact that mTBI has on neuropsychological functioning relative to moderate-to-severe head injuries. Even the most promising prospective studies are often hampered by significant selection biases (i.e., oversampling from emergent care settings and attrition in longitudinal designs), less effective use of appropriate controls, and not controlling for potential confounds [146].

Despite these limitations regarding mTBI, there are several tenets that can be drawn from the literature, and we address these below.

Tenets of Mild Traumatic Brain Injury

mTBI Tenet 1: Injury Severity Is Related to Outcome

In a series of widely recognized studies [147, 148], it was demonstrated that both cognitive and functional outcomes following head injury are related to severity of TBI, with mTBI having better outcomes and severe TBI having the worst outcomes. The strength of these studies is that a large number of patients ($N = 436$), with various injury severities, completed assessments at 1- and 12-months post injury with minimal attrition. In addition to the within-subjects comparisons, their patients were also compared to a matched trauma control sample ($N = 132$) also evaluated at 1-month and 1-year post injury. Patients with a history of TBI increasing in severity from moderate to severe, as measured by increased time to follow commands (the motor score from the GCS), had an incrementally greater chance of having more widespread and persisting neuropsychological and functional impairments 1 year post injury. Among patients with a history of mild head injury (time to following commands <1 hour), however, baseline performance on neuropsychological testing was similar to trauma controls at 1 month [147], and the vast majority were noted to experience good psychosocial outcomes 1 year post injury [148].

mTBI can occur in the context of other factors such as positive CT findings (e.g., "complicated mTBI" [focal brain lesion, skull fracture, etc.]), and this may further cause difficulties in recovery. In keeping with the inverse relationship between injury severity and outcome, patients with a history of complicated mTBI appear to have poorer cognitive function within the first month following mTBI than patients with uncomplicated mTBI [149]. Kwok and coauthors [150] evaluated complicated mTBI patients ($N = 31$) with GCS scores ranging from 13 to 15 with abnormal CT scans (skull fractures, hematomas, subarachnoid hemorrhage) and found persisting impairments in attention at 3 months. The performance of patients with a history of complicated mTBI has also been compared to the performance of patients with a history of moderate TBI. In this study, patients with a history of complicated mTBI ($N = 102$) and moderate TBI ($N = 127$) underwent neuropsychological testing at discharge from a rehabilitation facility and after 1 year. At both time points, there were noteworthy similarities between the mTBI and moderate TBI groups, with mTBI patients evidencing less severely impaired cognitive processing speed. Both groups were also noted to have incomplete recovery in functional status at the 1-year fol-

low-up visit, with no differences found between the groups [151]. There remains some debate as to whether complicated and uncomplicated mTBI patients should be pooled together in studies, or if those with complications should be viewed as a separate diagnostic group.

mTBI Tenet 2: Symptoms Immediately Following an mTBI Are Varied and May Occur Across Cognitive, Physical, and Affective Domains

Self-report symptom inventories (e.g., Rivermead Post-Concussion Symptoms Questionnaire [RPQ], Standardized Assessment of Concussion [SAC], etc.) have been utilized in the period following mTBI and in a variety of different settings [152–154] for review of various inventories). The most frequent subjective complaints following mTBI include headache, dizziness, irritability, poor concentration, fatigue, and memory loss, with the majority of symptoms resolving within 1 month [155, 156]. Across multiple factor analytical studies, these varied symptoms have been noted to load onto cognitive, physical, and affective clusters, although there is some debate as to whether a single factor that some label "concussion" better accounts for the symptoms [152, 157, 158]. A similar pattern of symptoms has also been described in the sports concussion literature, with headache, dizziness, sensitivity to light, and cognitive difficulties (e.g., slowed cognitive processing speed, memory difficulty) reported in the period following mTBI [156].

mTBI Tenet 3: The Vast Majority of mTBI Patients Will Experience Full Cognitive Recovery Within 3 Months

It is generally accepted that among patients sustaining an mTBI, the majority of symptoms resolve during the first week following the injury, with nearly complete resolution of most symptoms for most patients occurring within the first 3 months following the injury [159–161]. Consistent with this, the WHO has concluded the best evidence suggesting: "there are no mTBI-attributable, objectively measured, cognitive deficits beyond 1–3 months post-injury in the majority of cases" [146]. The WHO based their conclusions on a critical review of the literature and parallels the findings from meta-analytic studies evaluating patient performance on cognitive testing following mTBI. Binder and coworkers [143] included studies evaluating the cognitive functioning in adults (11 studies, 314 patients, 308 controls) at least 30 days following mTBI. The overall effect size of cognitive deficits was significant but small (d = 0.18), although a more conservative g statistic was notably smaller and not significant (g = 0.07). Patient performance on cognitive testing was further analyzed using neuropsychological domains of attention, memory acquisition, and performance skills (only three domains were examined across enough of the studies to allow for meaningful analyses). Among these three, only attention emerged as impaired following mTBI with a small effect size (g = 0.17). The authors also found it worthwhile to determine the positive and negative predictive values (PPV and NPV) of neuropsychological testing in patients with mTBI in the reviewed studies, as the detection of more subtle cognitive difficulties is more difficult than obvious neurological impairments. Given the low prevalence of persisting attention impairments based on their data (5%), the likelihood of accurately classifying mTBI with abnormal performance on cognitive measures, even with unrealistic sensitivity and specificity for the cognitive instruments (e.g., 0.9), was small at 0.32, and with smaller sensitivity and specificity test values, the PPVs continued to decrease. In contrast, the NPV of these cognitive measures was consistently high at all sensitivity and specificity levels (>0.98), suggesting much higher accuracy when diagnosing no persisting brain injury following mTBI based on neuropsychological measures.

More pronounced impairments in attention following mTBI have been reported in recent prospective studies (e.g., [150, 162]). Landre and coworkers [162] found mTBI patients (N = 37) to perform worse on measures of vigilance, attention, and memory relative to trauma patients (N = 32) approximately 5 days post injury. The effect sizes for these group differences were in the moderate-to-large range. Interestingly, both

mTBI and the trauma controls reported few concussion symptoms following their injury, and pain levels were controlled for and found not to be associated with cognitive performance in either group. That more pronounced cognitive impairments are found in some studies (e.g., [162]) but not others (e.g., [143]) may, in part, be related to the timing of neuropsychological evaluations relative to the onset of the head injury. For example, in the Binder and coworkers [143] meta-analysis, only studies evaluating cognitive performance 3 months post injury or later were included, whereas other studies may focus on patient cognitive performance within the first or second week following mTBI. Consistent with this, Schretlen and Shapiro [161] examined the effect of mTBI on cognitive performance across different time points post injury. In their meta-analysis, cognitive performance varied as a function of time, with a significant medium effect size reported among patients tested during the first 6 days post injury ($d = 0.41$, mTBI patients performing at the 33rd percentile of matched controls) and a smaller, but significant, effect size reported among patients tested 7–29 days post injury ($d = 0.29$). Patients tested 1–3 months post injury and after 3 months post injury demonstrated no differences from controls. Belanger and coworkers [163] demonstrated a similar finding, with small performance declines across seven of eight cognitive domains for mTBI patients evaluated acutely (<90 days) relative to those mTBI patients evaluated postacutely (≥90 days). Interestingly, in this meta-analysis, there was variability in performance across domains for those mTBI patients evaluated acutely, with the most pronounced effects of mTBI for delayed memory and verbal fluency.

Athletes may be a unique sample as they have extra incentive to have their symptoms improve quickly. In a large sample of college football players prospectively evaluated prior to mTBI and at several time points post injury, more severe symptoms were noted immediately following the mTBI and patterns of symptom recovery emerged as early as 3 hours post injury [164]. Within 7 days post injury, there were no differences relative to baseline scores or matched controls. It is important to mention that there are noteworthy differences between the general population and athletes evaluated in the sports concussion literature, as "motivation to return to play" in the latter may result in underreporting of mTBI symptoms. This likely explains the interesting finding that athletes report faster resolution of symptoms relative to those in the general population, as 85% of athletes reported full symptom recovery within 1 week and fewer than 3% reported symptoms beyond 1 month (see NCAA Concussion Study; [164]), in contrast to an appreciably higher proportion reported in the nonsports concussion literature (e.g., 8–33%; [144, 156, 165]).

mTBI Tenet 4: A Significant Minority of Patients Will Experience Persisting Postconcussive Syndrome Symptoms

It is important to note that individual patients may experience variability, both in terms of rate of recovery during this time period as well as between various symptom clusters [148, 156]. For a "significant minority," there may be mTBI symptoms that extend beyond the expected 3-month recovery period [143, 163]. The persistence of symptoms following mTBI is known as postconcussion syndrome (PCS) (e.g., symptoms persisting typically greater than 3 months post injury), although the nature and reasons for persistence of these symptoms is the source of much debate. The relationship between reported symptoms immediately following mTBI and persistence of postconcussion symptoms remains unclear, in part because there are few studies consistently and systematically evaluating these factors in the literature [146]. There is emerging evidence that suggests that PCS symptoms lasting longer than one year may be related to psychiatric factors as those discussed above rather than the head injury [49–51].

There is limited evidence to suggest that headache and dizziness in the emergency room and dizziness 2 weeks post injury may be predictive of persisting concussion symptoms [166, 167]. However, it is also important to note that many symptoms associated with concussion are also endorsed at high rates in other populations. Headache, fatigue, forgetfulness, frustration,

irritability, concentration difficulty, and sleep disturbance are among many overlapping symptoms reported at high rates and varying severity in college [168], claimant [165], adult control [169], and chronic pain populations [156, 170], although typically at lesser severity levels than those with mTBI within the first month postinjury [146]. In a landmark study that supports a cognitive-behavioral conceptualization for PCS etiology and informs current mTBI treatments, Mittenberg and coworkers [171] suggest that patients have preinjury *expectations* about mTBI symptoms and these, in turn, have the potential to become self-fulfilling. This was based on their finding that healthy adults endorsed symptoms they would expect to have 6 months following an mTBI at similar levels to patients with PCS (i.e., both reported similar levels of anxiety, depression, irritability, fatigue, memory difficulty). Additionally, when PCS patients were asked to estimate the same symptoms prior to their own injuries, compared to a healthy adult sample rating current symptoms, the PCS patients consistently reported fewer preinjury problems. Thus, it is hypothesized that PCS patients have expectations regarding TBI, which have the potential to form internal representations about outcomes. These representations have the potential to become self-fulfilling and may augment perceived intensity and frequency of PCS symptoms [126].

While postconcussion symptoms have been weakly linked to prognosis, multiple studies have demonstrated that compensation-seeking behavior is associated with persistence and severity of impairments as well as a delayed return to work and slowed recovery following mTBI [146, 172, 173]. Belanger and coworkers [163] found that, across studies, clinic-based samples including patients engaged in litigation were likely to have greater cognitive sequelae ($d = 0.74$ after 3 months) and that litigation was negatively associated with improvement of cognitive functioning over time. Conclusions related to the nature of this relationship are not addressed by correlative studies; the association could plausibly reflect more severe impairment independently leading to compensation seeking. Other moderating factors that have been less reliably related to PCS include being female, off-work due to injury, and a history of psychiatric illness. Prior psychiatric illness has also been identified as a risk factor for acute stress disorder following a motor vehicle collision, and this is, in turn, a predictor of the later development of PTSD [146].

mTBI Tenet 5: Neuropsychological Assessment Must Incorporate Both Performance Validity Test (PVT) and Symptom Validity Test (SVT) Measures

The importance of assessing respondent validity has been emphasized by the national boarding organizations of neuropsychology (e.g., the American Academy of Clinical Neuropsychology [AACN] and the National Academy of Neuropsychology [NAN]), with both organizations issuing position papers detailing the importance of including both stand-alone and embedded measures of symptom/performance validity in neuropsychological evaluations [174, 175]. It is important to note that studies have demonstrated how the potential for external incentives [172] and/or poor effort [176] can negatively influence the test results more than the extent of neurological involvement. Similarly, the influence of effort has also been shown to account for a significant portion of variance related to cognitive test performance in veterans reporting mTBI and PTSD symptoms [177]. This recommendation for PVT and SVT use should not be viewed as pejorative, as the use of these measures primarily informs the validity of the testing data rather than the intent of underlying test-taking behavior. It should also be noted that magnification of symptoms and/or PVT failure is not uncommon in the veteran population [178–182]. Given the nature of neuropsychological and psychological evaluations, which are used both to establish current functioning and inform optimal treatments, it is essential to draw on multiple sources of information, and this includes consideration of both PVT and SVT data.

Conclusion: Behavioral and Psychiatric Comorbidities of TBI

Extensive evidence associates TBI with psychiatric and behavioral sequelae. While the design of these studies makes it often difficult to differentiate symptoms based on severity of injury, premorbid deficits, and functioning from the contribution of the, it seems very likely that, at the minimum, TBI is a risk for accentuating premorbid behaviors [106], and individual cases indicate the potential for profound behavioral change [101]. The mechanism of these effects has not been examined, although changes in self-regulation and social information processing may result from neurological insult, psychiatric symptoms, or substance use. On the other hand, it is also conceivable that psychiatric disorder and TBI become difficult to distinguish from an epidemiological perspective, given that circumstances may put an individual at risk for both [38]. In this case, prospective studies and treatment interventions will be needed to identify the salient underlying disorders. Several research groups are pursuing a variety of imaging, neuropsychological, and treatment studies to identify characteristics that would contribute to this distinction. In the interim, it is important from a patient care perspective to identify treatable behaviors that are causing distress to the patients or those around them. While definitive evidence for efficacy is in many cases lacking, a number of reasonable suggestions or extrapolations from other conditions have been reported that provide a starting point to develop a treatment plan. However, lack of definitive evidence for efficacy or the possibility of a unique sensitivity to adverse events affecting TBI patients suggests that treatment should be approached with an appreciation for potential difficulties.

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Chronic Effects of TBI in a Military Population

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Abbreviations

AMEDD	Army Medical Department
ATs	Astrocytic tangles
AUDIT	Alcohol Use Disorders Identification Test
CTE	Chronic traumatic encephalopathy
dlPFC	Dorsolateral prefrontal cortex
DoD	Department of Defense
DVBIC	Defense and Veterans Brain Injury Center
FY	Fiscal year
GOS	Glasgow Outcome Scale
HC	Healthy controls
HRQOL	Health-related quality of life
IED	Improvised explosive device
IPU	Integrated Practice Unit
MHS	Military Health System
MPS	Multiple physical symptoms
mTBI	Mild traumatic brain injury
MTF	Military Treatment Facilities
NDAA	National Defense Authorization Act
NFTs	Neurofibrillary tangles
NICoE	National Intrepid Center of Excellence
NSI	Neurobehavioral symptom Inventory
OEF	Operation Enduring Freedom
OFS	Operation Freedom's Sentinel
OIF	Operation Iraqi Freedom
OIR	Operation Inherent Resolve
OND	Operation New Dawn
PCL-C	Posttraumatic stress disorder checklist
PDHA	Post Deployment Health Assessment
PDHRA	Post-Deployment Health Re-Assessment
PH1	VHIS Phase 1
PH2	VHIS Phase 2
PH3	VHIS Phase 3
PH4	VHIS Phase 4
PNS	Polytrauma Network Sites
PPCS	Persistent post-concussive symptoms
PRC	VA Polytrauma Rehabilitation Center

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PSC	Polytrauma System of Care
PSCT	Polytrauma Support Clinical Team
PTE	Posttraumatic epilepsy
PTSD	Posttraumatic stress disorder
TAC	TBI Advisory Council
TBI	Traumatic brain injury
TBI-CareQOL	Health-Related Quality of Life in Caregivers of Service Members with Military-Related Traumatic Brain Injury
TBI-QOL	Traumatic Brain Injury Quality of Life
TC	Trauma controls
VA	Department of Veterans Affairs
VA's PT/BRI QUERI	VA's Polytrauma and Blast Related Injury Quality Enhance Research Program
VHA	Veterans Health Administration
VHIS	Vietnam Head Injury Study
VISN	Veterans Integrated Service Networks
vmPFC	Ventromedial prefrontal cortex
WRAMC	Walter Reed Army Medical Center
WRNMMC	Walter Reed National Military Medical Center

Scope of the Problem

Traumatic brain injury (TBI) affects military service members during times of both war and peace [1]. Between 2000 and 2018 Q1, 383,947 service members have sustained at least one TBI. Of these TBI, 82.3% were classified as mild, 9.7% as moderate, 1.1% as severe, 1.4% as penetrating, and 5.6% as not further classified [2]. While data on the exact number of troops deployed or number of individual deployments in support of Operations Iraqi Freedom (OIF), Enduring Freedom (OEF), New Dawn (OND), Inherent Resolve (OIR), and Freedom's Sentinel (OFS) is unclear, there are 4,398,000 living veterans who have served since 2001 [3]. Compared to civilians, active duty service members and reservists are more likely to sustain a TBI [1]. Through June 2014, there were approximately 2.65 million deployments. Of that number, 1.2 million individuals were deployed more than once. These combat deployments increase the risk of TBI among service members [4].

During the period from April 1, 2003, to June 30, 2014, there were 2,020,340 deployments to Iraq/Afghanistan by active component members who had not previously been diagnosed with TBI. Within 3 years after returning from these deployments, there were 191,052 TBI diagnoses; the cumulative incidence of post-deployment TBI diagnoses was 9.46 per 100 deployments. Among all demographic/military subgroups of Iraq/Afghanistan deployers, the cumulative incidence of TBI diagnoses was highest among those who were serving in the Army (11.90 per 100 deployments), older than 24 years (25–35 years and older than 35 years: 10.28 and 10.32 per 100 deployments, respectively), and in combat-specific occupations (10.68 per 100 deployments) [5]. Data from the Department of Veteran's Affairs Polytrauma and Blast-Related Injury Quality Enhance Research Program (PT/BRI QUERI) reflect that 9.8% of veterans of the Iraq and Afghanistan wars who sought care in the Veteran's Health Administration (VHA) between FY 2010 and FY 2012 had TBI diagnoses [6]. Rate of diagnosis by fiscal year from 2009 to 2014 was about 7%: 2009 was 6.7% of 327,388 total [7]; 2010 was 6.8% of 398,453 total [8]; 2011 was 6.5% of 471,383 total [9]; 2012 was 6.8% of 525,307 total [6]; 2013 was 7.1% of 607,330 total; and 2014 was 7% of 684,133 total [10]. Data from self-report and various surveys following deployment suggests that prevalence rates of TBI in service members are estimated to be between 10 and 20% [11–13]. When compared to another health condition of concern to the military, posttraumatic stress disorder (PTSD), there were 2,279,258 deployments to

Iraq/Afghanistan by active component members who had not previously been diagnosed with PTSD in that same time period. Within 3 years after returning from war zone deployments, there were 110,618 PTSD diagnoses; the cumulative incidence of post-deployment PTSD diagnoses was 4.85 per 100 deployments. When demographic/military subgroups were examined, cumulative incidence rates of PTSD diagnoses were highest among those in healthcare and combat-specific occupations (8.52 and 5.62 per 100 deployments, respectively) [5].

The exact risk of TBI attributable to military service is unclear. The overall incidence of TBI-related hospitalization in the Army decreased 75% in the 1990s. Additionally, while the rates for all TBI severity levels decreased, the rate for mild TBI decreased more than for moderate and severe TBI. In the early 1990s, the Army's TBI hospitalization rates were generally higher than civilian rates, but by the late 1990s, most of the Army's rates were lower than or equal to the civilian rates. This may be related to effective injury prevention programs or changes in the Army population in that time period [14]. By the time of the war period, injury in theater (another term for a deployed setting) was estimated to account for fewer than half of all post-deployment diagnoses of TBI, even though TBI diagnosis rates attributable to combat theater service sharply increased from the beginning of the ground war in Iraq through 2007–2009 and then stabilized. Rates and proportions of TBI diagnoses attributable to enhanced ascertainment also markedly increased during the war period. These increases began about 2007–2009 and corresponded to marked changes in TBI policies and programs. It has been suggested if current policies related to TBI case detection continue, the end of active military operations will not significantly decrease rates of TBI diagnoses. As war injuries only accounted for slightly more than one third of all post-deployment TBI diagnoses in 2012–2013, diagnosis rates after the war may be twice as high as those before the war [5]. See Fig. 1.

In the most recent conflicts, the primary mechanism of combat-related TBI is blast exposure. Returnees who report symptoms of mild TBI (mTBI) through surveys indicate being injured by a blast/explosion more so than any other mechanism [11, 15]. Data from the post-deployment health assessment (PDHA) showed that blast was identified as a mechanism for 45.7% of those who endorsed questions suggestive of TBI, with most explosions less than 25 meters away [16]. A blast TBI results from the service member being "exposed" to an explosive, such as an improvised explosive device (IED), rocket propelled grenade, land mine, artillery, or bombs that then results in a TBI [17]. This exposure can theoretically result in a TBI through direct effects of a blast [18, 19], although

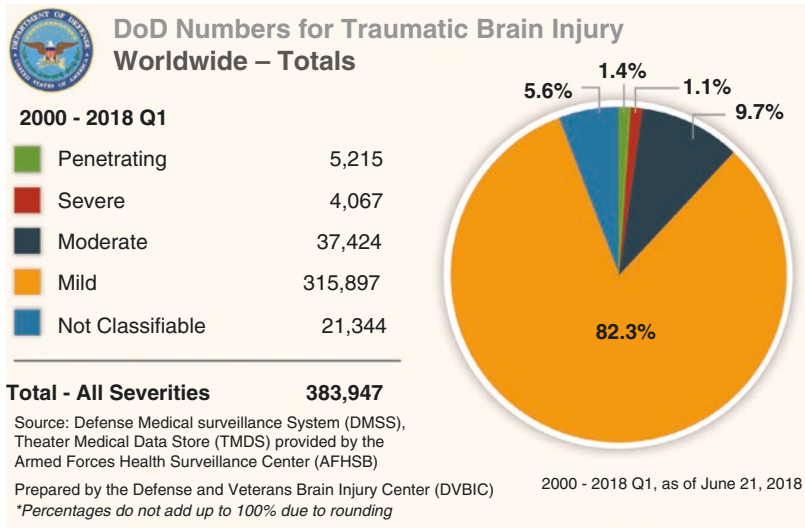

Fig. 1 DoD numbers for traumatic brain injuries, Worldwide Totals. 2000–2018 first Quarter. (Public Domain. Source: http://dvbic.dcoe.mil/files/tbi-numbers/worldwide-totals-2000-2018Q1-total_jun-21-2018_v1.0_2018-07-26_0.pdf)

that is quite rare in clinical practice [20]. In recent years, injury due to blast has received significant attention [17, 21–23] leading one to believe that this is a new injury mechanism. However, the effects of explosions on the brain were described as early as 1916 in the medical literature [24]. Explosions were also a significant source of injury in World War I and World War II, accounting for 35% and 73% of the injuries, respectively [25]. The cluster of symptoms that became known as "shell shock" was originally thought to be related to blast exposure, although the idea was controversial even during World War I and in the years after [26].

Blast, as a mechanism of injury for TBI, has some characteristics that play a role in symptom presentation, while other aspects share significant characteristics with other, more typical injury mechanisms. This, at least in part, is related to the contribution of mechanical forces in blast injury [27, 28]. Blast has been used to guide treatment and structure treatment teams in Veterans Affairs medical treatment facilities, given the characteristics shared by many with blast injury [29]. In one sample seen in the Department of Veterans Affairs polytrauma system, the pattern of injuries was different among those with injuries due to blasts versus other mechanisms. Injuries to the face (including eye, ear, oral, and maxillofacial), penetrating brain injuries, symptoms of posttraumatic stress, and auditory impairments were more common in blast-injured patients than in those with injuries of other etiology [30]. Experience with other patients at a Veterans Affairs polytrauma rehabilitation center (PRC) showed a broader spectrum of physical injuries, higher levels of admission and discharge opioid analgesic use, reduced improvement in pain intensity following treatment, and much higher rates of PTSD and other psychiatric diagnoses in those injured through blast as opposed to other mechanisms in which a blast was not involved [31]. This observation is consistent with the Israeli experience, in which civilian victims of blast-related terror attacks have more body regions injured than those injured through other mechanisms and are more severely injured overall [32]. Neuropsychological profiles and symptom reporting have not generally shown differences between the two groups, however [33–36].

Why Is Looking at Chronic Effects of Military TBI Important?

In FY 2014, individuals with a TBI diagnosis had higher rates of healthcare utilization and a higher cost of care than those veterans who did not carry a TBI diagnosis [10]. The major driver for this differential is reflected in the rehabilitation lengths of stay which average 36.4 days for polytrauma rehabilitation, 63.6 days for transitional rehabilitation program, and 26.4 days for all other rehabilitation medicine inpatient care [10].

When considering the chronic effects of TBI, it is important to consider the environmental factors which influence TBI rehabilitation and recovery in military and civilian populations, as well as the severity of the injury, the access to services, the co-morbid health conditions, and other factors. Outcome studies in mTBI have typically described civilian populations, but there may be differences in the military population or in mTBI acquired under combat conditions. A more extensive description of mTBI (concussion) and its consequences can be found in other chapters. In general, however, mTBI is known to result in a variety of acute symptoms. These symptoms, while they may cause significant distress and affect functioning, are generally time-limited and resolve without lasting consequences [37–39]. The World Health Organization Collaborating Center Task Force on mTBI published a meta-analysis that suggests the majority of adults with uncomplicated mTBI have good outcomes and generally recover fully within months [40]. Additionally, any cognitive deficits identified in neuropsychological testing typically resolve within one to 3 months [41].

This clinical course, well described in the civilian literature, shows significant parallels in the military population [42–45]. This recovery occurs even under the adverse circumstances

associated with a deployed environment. One Brigade Combat Team (BCT) deployed to Iraq (n = 3973) with 907 soldiers with at least one clinician-confirmed, deployment-acquired mTBI was further evaluated regarding sequelae. Those with TBI were significantly more likely to recall somatic and/or neuropsychiatric symptoms immediately post-injury and endorse symptoms at follow-up than were soldiers without a history of deployment-related TBI. A total of 33.4% of soldiers with TBI reported three or more symptoms immediately post-injury compared with 7.5% at post-deployment, suggesting significant resolution of symptoms even in a deployed setting [46].

However, some longer-term data suggest that recovery may not be as benign or rapid in those with mTBI acquired in a combat setting. In one large, prospective cohort study, active-duty US Military personnel evacuated from Iraq or Afghanistan to Landstuhl Regional Medical Center from 2010 to 2013 were enrolled. The groups consisted of those with blast plus impact TBI (n = 53), non-blast-related TBI with injury due to other mechanisms (n = 29), blast-exposed controls evacuated for other medical reasons (n = 27), and non-blast-exposed controls evacuated for other medical reasons (n = 69). All patients with TBI met Department of Defense (DoD) criteria for concussive mTBI. The study participants were extensively evaluated in follow up 6–12 months after their injury. Both TBI groups had higher rates of moderate to severe overall disability than the respective control groups: 41/53 (77%) of blast plus impact TBI and 23/29 (79%) of non-blast TBI vs. 16/27 (59%) of blast-exposed controls and 28/69 (41%) of non-blast-exposed controls. Overall outcomes were most strongly correlated with depression, headache severity, and number of abnormalities on neuropsychological testing, but a substantial fraction of the variance in outcome was not explained by any of the assessed measures [47]. In a related sample seen by the same study group [48], 38 subjects with blast-related concussive TBI and 34 controls were enrolled and evaluated in Afghanistan in 2012. All subjects returned to duty and did not require evacuation. The subjects were evaluated again 6–12 months later in the United States. Acute assessments revealed heightened post-concussive, posttraumatic stress, and depressive symptoms along with worse cognitive performance in subjects with TBI. At follow-up, 63% of subjects with TBI and 20% of controls had moderate overall disability. The service members with TBI showed more severe neurobehavioral and depressive symptoms, posttraumatic stress, and more frequent cognitive performance deficits than control subjects. Significant headache impairment was also noted. Logistic regression modeling using only acute measures identified that a diagnosis of TBI, older age, and more severe posttraumatic stress symptoms provided a good prediction of later adverse global outcomes. Overall, those with concussive blast-related TBI in Afghanistan who returned to duty still showed significant dysfunction on many clinical outcome measures 6–12 months after injury. It was concluded that the poor global outcome appeared to be driven by psychological health measures, age, and TBI status. See Fig. 2.

Even in those without TBI, military deployment can result in increased emotional distress or overt psychiatric disorders [49, 50]. One large, population-based, longitudinal descriptive study of an initial large cohort of 88,235 US soldiers returning from Iraq who completed both a PDHA

Fig. 2 US Marine provides assistance during a fire team training. (Public Domain. Source: https://core.wazeedigital.com/video/clip/779W83I_92L8AOOHZ.do?assetId=asset_16396884/clip_39564614)

and a Post-Deployment Health Re-Assessment (PDHRA) reported more mental health concerns and were referred at significantly higher rates from the PDHRA than from the PDHA. Based on the combined screening, clinicians identified 20.3% of active and 42.4% of reserve component soldiers as requiring mental health treatment. Soldiers also frequently reported alcohol concerns [51]. More recently, Vasterling and colleagues [52] prospectively examined PTSD as a long-term consequence of deployment, integrating data collected from 2003 to 2014. PTSD symptoms in US Army soldiers were assessed in 598 service members and military veterans with a median of 7.9 years after an Iraq deployment. At long-term follow-up, 24.7% of participants met the case definition for PTSD, which represented an increase of 14.2% from the percentage assessed post-deployment and of 17.3% from the percentage assessed pre-deployment. They concluded that PTSD is an enduring consequence of war zone participation among military personnel and veterans and that adverse stress reactions cannot necessarily be expected to dissipate over time. For those injured, the rates are even greater [11, 53, 54].

Systemic injury in combination with TBI has been termed "polytrauma." A polytrauma triad has been reported [55] with rates of chronic pain, PTSD, and persistent, post-concussive symptoms (PPCS) present in 81.5%, 68.2%, and 66.8% of one sample, respectively. From this study, only 3.5% of the individuals seen were without chronic pain, PTSD, or PPCS, and 42.1% of the sample were diagnosed as having all three conditions concurrently. In the polytrauma population, this introduces significant challenges for care and requires a multidisciplinary, integrated approach for success to be achieved [56]. Data from the VA reflect a high incidence of TBI in those with significant bodily injury [57]. Of 188 consecutive patients admitted to a Veterans Affairs PRC between 2001 and 2006, 93% were diagnosed with a TBI in addition to their other injuries. Pain disorders and mental health conditions were noted to have a high rate of co-occurrence (100% and 39%, respectively).

The prevalence of polytrauma in the blast population may complicate the recovery for those who, under the best of circumstances, would otherwise have an uneventful recovery from their mTBI. In a civilian population, those who sustained an mTBI with minimal extracranial injuries and reported low pain post-injury were more likely to return to work following mTBI than those who had extracranial injuries associated with the mTBI [58]. Of those that suffered extracranial injuries, 44% were still in treatment 6 months post-injury, as opposed to only 14% of those who had minimal extracranial injuries. Additionally, those with extracranial injuries resumed work less frequently than their counterparts and reported more physical limitations. Finally, those who engaged in continued rehabilitative treatments reported significantly more severe post-concussive symptoms. Polytrauma patients, even without brain injury, have high rates of neurobehavioral symptoms, including memory difficulties, irritability, mood swings, suspiciousness, amotivation, and guilt [59].

This relationship is not straightforward, however. Some research has shown that there tends to be an inverse relationship between post-concussion symptom reporting and bodily injury severity; that is, as injury severity increases, the frequency of post-concussive symptoms decreases [60, 61]. This finding has been replicated [62] in a larger sample of 579 US military service members who sustained an uncomplicated mTBI with concurrent bodily injuries. There was a significant negative association between injury severity scores and symptoms on the Neurobehavioral Symptom Inventory (NSI) and the Posttraumatic Stress Disorder Checklist-Civilian (PCL-C). Further examination of the relationship between symptom reporting and injury severity across six body regions showed that injuries to the face, abdomen, and extremities were significant predictors of the NSI total score. The face and extremities were significant predictors of the PCL-C total score. Overall, there was an inverse relation between bodily injury severity and symptom reporting in this sample. The authors hypothesized several possible explanations, including underreporting of symptoms, increased peer support in some subjects, disruption of fear conditioning because of acute morphine use, or delayed expression of symptoms.

PTSD and chronic depression frequently coexist with mTBI cases in the military [11] and show considerable overlap in symptoms and in co-occurrence with TBI [11]. TBI has been shown to complicate or prolong recovery from preexisting or co-morbid conditions such as PTSD [63]. Post-concussive symptoms may actually increase the likelihood of developing PTSD, because these symptoms interfere with adequate adjustment to the event [64]. In addition, cognitive or neurobehavioral impairments associated with TBI may influence the efficacy of treatments for PTSD or other mental health conditions. Psychotherapeutic or educational strategies may require intact cognition to work maximally. Even subtle attentional or memory difficulties might affect learning or other aspects of the treatment process. Likewise, PTSD and depression confound mTBI diagnosis in their ability to influence self-report of symptoms [65] and also mediate persistent symptoms reported by mTBI patients [11, 65, 66]. Multiple studies [63, 67–72] have described the relationship between TBI and posttraumatic stress symptoms. It is clear that psychiatric symptoms play a strong role in the perpetuation of post-concussive symptoms, their expression, and the recovery process in the individual patient. As one moves further from the point of injury, the more difficult it becomes to divide the relative contribution of the post-concussive and emotional symptoms to the clinical presentation.

While the majority of TBIs sustained in theater are mild, TBIs of greater severity (especially severe closed and penetrating) are the injuries that often cause impairments that are prolonged or permanent in nature and can impact the service member's long-term quality of life [73–76]. Additionally, these injuries usually require significant post-injury inpatient care and rehabilitation [77]. See Fig. 3. While variable, more severe TBI typically results in worse outcomes [78–80] in multiple domains including recovery of motor function [81], cognition [41], and behavior and mood, among other things [82–87]. This is the case for both civilian and military populations.

There have been a number of studies involving health-related quality of life (HRQOL) after moderate-severe TBI in the civilian population.

Fig. 3 US Army soldier balances on a beam with a physical therapy assistant. (Public Domain. Source: https://core.wazeedigital.com/video/clip/75M187590_x01.do?assetId=asset_16376703/clip_35533065.)

In comparing short-term and long-term HRQOL following moderate-severe TBI, studies have found HRQOL is generally worse as compared to healthy controls in physical health, mental health, social functioning, emotional well-being, pain, communication, body care and movement, and general health [74, 75, 88]. Interestingly, in comparing physical and psychosocial domains at 1 year post-injury between TBI and trauma control patients, the HQROL is similar [88].

The time course and trajectory of recovery varies with the population being studied. Hu and colleagues [74] found overall physical domain HRQOL improvement, but only some mental health domain improvement comparing from time of hospital discharge to 6 months post-injury. At 12 months post-injury, all mental health domains showed improvement. Other studies have shown only modest change post-acutely. There were no overall HRQOL changes

between 2 and 8 years post-moderate-severe TBI [75]. In a study with a sample of mixed TBI severity, Pagulayan and colleagues [88] found that patients post-TBI reported overall HRQOL improvement from 1 month to 6 months post-TBI; however, the majority of the improvements were related to physical HRQOL. By 3–5 years post-TBI, there were some improvements noted in both physical and psychosocial HRQOL. Lippert-Grüner and colleagues [89] investigated how HRQOL was affected for polytrauma patients following severe TBI at 6 and 12 months post-injury. Groups were comprised of those with severe TBI with co-morbid polytrauma and those with severe TBI and no polytrauma. Both groups showed improved HRQOL from 6 to 12 months post-injury, and the only difference found was HRQOL in relation to physical functioning. Those with severe TBI and co-morbid polytrauma reported worse physical functioning than those severe TBI patients without polytrauma.

There have been many fewer studies of the longitudinal course in military populations.

The most comprehensive long-term study of service members who sustained a TBI in wartime is the Vietnam Head Injury Study (VHIS). This retrospective/prospective longitudinal study examined the effects of TBI, especially penetrating TBI, on Vietnam War veterans [90]. The VHIS registry enrolled 1221 Vietnam veterans who had sustained a TBI between 1967 and 1970. The majority of the veterans in this study sustained penetrating TBI due to low velocity fragments that penetrated service members' skulls during the conflict [91].

Phase 1 (PH1) of the study was the retrospective component of the study that reviewed the medical records of service members from 5 years post-injury. Phase 2 (PH2) took place 15 years post-TBI. This sample consisted of 520 participants from PH1 and 85 Vietnam veteran controls who were uninjured in the conflict. Of PH2 participants, 92% had penetrating head injuries. PH2 consisted of a week-long visit to Walter Reed Army Medical Center (WRAMC), Washington, DC, for a comprehensive evaluation which included neuropsychological, language, neurological, and neuroimaging assessments [90].

VHIS Phase 3 (PH3) took place 35 years post-TBI and included 182 participants from PH2. In this phase, participants completed neuropsychological, psychiatric, neurological, and imaging assessments at the National Naval Medical Center, Bethesda, MD. Phase 4 (PH4) occurred approximately 40–45 years post-injury at the National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD. PH4 included genetic testing and assessments similar to those of PH2 and PH3 [90].

There were several major findings from PH1. The first was neurosurgical. It was determined that cranioplasty after penetrating TBI should take place over a year post-injury to ensure the best outcomes and control morbidity rates. Additionally, it was observed that many of the veterans who sustained severe penetrating TBI did not have an extended loss of consciousness (LOC). Over 50% of those injured had no or brief LOC, and over 40% did not have posttraumatic amnesia [92].

In PH2 the findings were more extensive. In the physical domain, it was observed that 53% of the post-injury veterans had a history of posttraumatic epilepsy (PTE) which had begun within 1 year post-injury. Of those with a history of PTE, about 50% were still experiencing seizures 15 years post-injury [93]. Study investigators were able to use the veterans' TBI and PTE histories to develop a formula to predict the time between an individual's injury and first seizure. This formula took into account factors, including the individual's state of consciousness, affected region of the brain, hematoma presence, aphasia presence, metal fragment remnants, and the seizure-free time post-injury [94]. At PH2 90 subjects suffered from hemiparesis [95]. Further examination of these subjects determined that TBI that affected the motor regions in either hemisphere of the brain had damaging effects to the ipsilateral motor capabilities of the upper extremity. These findings also concluded that the left hemisphere has a stronger role in bilateral motor processes [96].

In the cognitive domain, individuals studied at PH2 demonstrated that the amount of brain disruption caused by a TBI was a predictor of the recovery of daily functioning [90]. Additionally, when compared to controls at PH3, those with a history of TBI had a greater cognitive decline over time following their TBI. Intelligence of subjects pre-injury was the most reliable predictor of cognition post-injury [97].

About 24% of PH2 subjects experienced aphasia post-TBI, and, of those subjects, 34% had a cessation of the aphasia within 10 years. Over time it was found that sensorimotor aphasia progressed to motor aphasia and that while sensory aphasia often remained, motor aphasia resolved [98]. Brain lesion location was associated with semantic memory and visual and verbal episodic memory shortfalls [99]. In all subjects with TBI, short-term memory deficits were identified regardless of the location of the lesion or symptoms of substance dependence and depression [100].

Behaviorally, PH2 subjects demonstrated that social judgment may be impaired for those with prefrontal lobe lesions [101]. For those with right orbitofrontal lesions, anxiety and depressive symptoms were more common, whereas for those with left dorsofrontal lesions, increased anger and hostility were more likely [102].

Education and work outcomes were also assessed in PH2. The severity of the injury was found to impact the likelihood that a service member would return to school or work. For those who were able to return to work, the severity of injury did not play a role in the occupational roles held post-injury [103].

In PH3, specific lesions were examined for their behavioral correlates. It was found that the superior parietal cortex plays a significant role in working memory that involves rearranging and manipulating information. It did not play a role in working memory that involves information rehearsal or retrieval of long-term memory [104]. The ventromedial prefrontal cortex (vmPFC) played a large role in fatigue of the subjects. Those who had lesions of the vmPFC had greater fatigue than those who had lesions of the dorsolateral prefrontal cortex (dlPFC), those without frontal lesions, and healthy controls. The size of the lesion at vmPFC was also a predictor of the level of fatigue experienced by a subject [105]. Additionally, subjects who had left dorsomedial prefrontal cortex lesions were more likely to experience insomnia [106]. At PH3, vmPFC lesions were also associated with increased resistance to depression, while dlPFC lesions were associated with depression susceptibility [107]. Additionally, Koenigs and colleagues [108] found that PTSD treatment could involve inhibiting selective functions of the vmPFC and/or amygdala following TBI.

More recently, a longitudinal study at WRAMC examined neurobehavioral symptom reporting in service members following moderate-severe TBI [n = 52] over the course of 3 years post-injury [109]. During that time period, symptoms reported between baseline and follow-up visits were variable. Persistent symptoms over the course of 3 years reported by these service members included difficulties with memory, concentration, attention, poor sleep, and irritability. Headaches, sensitivity to noise, and irritability were the most common newly developed symptoms reported at follow-up. Overall, there was a substantial variability in symptom reporting between the baseline and follow-up visits. Depending on the subsample, 41.9–63% of the service members were symptomatic at both baseline and follow-up visits; however, from baseline to follow-up, there were 11.1–16.1% who reported no symptoms; 22.2–31.8% who reported symptom improvement, and 3.7–16.1% who reported the onset of new symptoms. This is consistent with the findings of the civilian longitudinal study of Dikmen and colleagues [110] in which many of the subjects who were symptomatic at baseline were not always those symptomatic at follow-up.

Examining specific symptoms and behaviors, a large portion of service members reported mental health problems that required ongoing treatment (18.2–48.1% depending on the time point). Many service members reported experiencing headaches (37.8–51.9%), bodily pain (40.7–50.0%), and problematic alcohol consumption

(22.2–32.3%). A majority of the service members reported continued medication use (71.0–88.9%). Anti-psychotics, depressants, and anxiety medications comprised 32.3–48.1% of those medications, and opioid or other pain medications comprised 31.8–51.9%. Of those taking medications, 64.5–81.5% reported that they found the medications to be effective. Regardless, overall health status was self-rated as "good," "very good," or "excellent" by 74.1–90.9%, and 81.5–90.9% rated that they were satisfied with their life [109].

Twelve months post-TBI had the largest number of service members receiving mental health treatment, which was consistent with the highest neurobehavioral symptom reporting also occurring at that time. Approximately 29% of service members 12 months post-TBI and 18.2% of service members 36 months post-TBI reported engaging in mental health treatment. Additionally bodily pain, usually in the upper extremities, body, or lower extremities, greatly increased between 12 and 24 months post-TBI. There were minimal changes reported in bodily pain at 36 months post-TBI. Problematic alcohol consumption was reported in 22.2–32.2% of service members across the 3-year, longitudinal period; however, only 3.7–9.1% of service member family members reported complaints regarding the service members' alcohol consumption. Additionally, 6.5–9.1% of service members reported suicidal or homicidal ideation [109].

At 12, 24, and 36 months post-injury, 4.62–53.8% of service members reported working full-time. At 36 months post-injury, 54.5% of service members were still active duty; of that group, more service members reported their work quality to be worse at 12 months post-injury than pre-injury [109].

While the reasons for this variability are not clear, it might be concluded that new-onset symptoms could be attributed to other factors, including co-morbidities, legal factors, social-psychological factors [111–116], psychiatric disorders, chronic pain, PTSD, or external incentives [64, 117–125]. Polytrauma patients have also been found to report the development of new symptoms over time [59]. The onset of these new symptoms could be the result of new symptoms caused by or magnified by the original symptoms. For example, if a patient is experiencing chronic pain, they may be more likely to experience poor sleep. Over time the combination of chronic pain and poor sleep hygiene could result in an increase in frustration, irritability, and depression [109].

Quality of Life Following TBI

HRQOL is a multidimensional construct reflecting the impact of a disease, disability, or its treatment, on mental, physical, and social well-being [126]. The importance of assessing HRQOL as an outcome variable following TBI is well recognized [127], although there are few studies in either military or civilian populations that address this issue. Service members with injuries can face long-term physical, emotional, social, and functional challenges that may impact their HRQOL [111, 128–132].

Examination of HRQOL after mTBI is fairly common in civilian studies [88, 133–137]. Unfortunately, there are few studies that have examined HRQOL in military service members following TBI [138–140], and most have been based on those with mTBI. In a large-scale survey of the Florida National Guard [140], self-reported mTBI/concussion during deployment was associated with ratings of poor overall post-deployment health. This association was more related to psychological health than physical health. In most military-related studies, psychological health issues in the injured population were more potent predictors of HRQOL than was injury status. One study [139] examined HRQOL in service members divided into four mutually exclusive groups stratified by mTBI and PTSD diagnoses. Measures related to physical health, health and social care, home/physical environment, and leisure activities were worst in a group with PTSD; the mTBI and control groups fared better. This is consistent with a later study [138], in which service members who screened positive for both mTBI and PTSD, or PTSD only, reported worse

HRQOL (i.e., SF-36) in both physical and mental domains compared to groups with just mTBI or control groups.

In another study conducted at WRAMC [62], service members with mTBI and concurrent bodily injuries were followed for up to 5 years post-injury to examine HRQOL. The study found that service members reported many ongoing symptoms within the first 5 years post-injury. Pain, not specific to any one region of the body, was one problem reported by a majority of service members. Since many study members sustained concurrent physical injuries with their mTBI, this finding was anticipated. A majority of service members also reported medication use throughout the 5 years post-injury. Medications were used to relieve symptoms, including pain, as well as the treatment of mental health symptoms. The need for continued behavioral health treatment was also reported by a majority of the sample. Furthermore, 5.6–14.8% reported the presence of suicidal or homicidal ideation at some point across the 5 years post-injury. This is consistent with other studies in this population where high rates of pain, mental health treatment, and medication use have been reported [11, 60, 61, 128, 130, 141–143].

Despite ongoing symptom reporting, a large portion of the 5-year Walter Reed sample [62] reported generally high satisfaction with life and rated their health status as generally good or better. Social relationships were also generally good, with a substantial number who reported being married and greater than 50% of the sample reported living with others, such as a friend or family members. Nonetheless, a substantial minority of service members reported that they required help with daily activities, particularly with tasks involving household chores and community-based errands. The need for help persisted even in the face of an overall improvement of disability status (as rated by the Glasgow Outcome Scale, GOS) from 6 to 60 months post-injury. Although 60–70% of the sample had returned to work within the first 4 years, only 30% of service members had returned to full-time work by 24 months post-injury, and fewer than 50% had returned to full-time work by 48 months, suggesting that the percentage may remain largely stagnant.

The "15-Year Studies"

The DVBIC was formed through Congressional language in 1992 and serves as a resource for military service members, their beneficiaries, and veterans affected by TBI. Congressional concern over long-term outcomes in those injured with TBI in the military prompted Congress to include language mandating a 15-year longitudinal study in Section 720, HR 5122 of the 2007 National Defense Authorization Act (NDAA). The language specifically required a longitudinal study on TBI sustained by service members in Operation Iraqi Freedom (OIF) and Operation Enduring Freedom (OEF). The study was to be conducted over a 15-year period and address (1) the long-term physical and mental health effects of TBI incurred by members of the Armed Forces during service in OIF and OEF; (2) the care and rehabilitation needs of these members with TBI; (3) the type and availability of care and rehabilitation programs and services within and outside the DoD and the Department of Veterans Affairs for these service members and veterans with TBI; and (4) the effect this injury has on family members and caregivers. Details of early findings and the study design can be found in the March 2013 report to Congress, "National Defense Authorization Act for Fiscal Year 2007, Section 721 3-Year Update Longitudinal Study on Traumatic Brain Injury Incurred by members of the Armed Forces in Operation IRAQI FREEDOM and Operation ENDURING FREEDOM, "The 15-Year Studies." The "Exploring the Natural History of Traumatic Brain Injury Within a Military Cohort – A Longitudinal Database and Blood Banking Study" was developed to study the effects of TBI within the military population over a 15-year period. This study, which will be referred to in this chapter as the Natural History Study, collects data from service members and veterans who sustained a TBI since October 2001, either while deployed in OIF/OEF or stateside. Control

groups include those with non-TBI injuries (orthopedic and soft tissue) and non-injured service members who have been deployed at least once in OIF/OEF. Data collected include clinical interviews, neurobehavioral symptoms, neurocognitive symptoms, neuroimaging, blood specimens, and sensory/motor data. This study is divided into two levels of engagement, a Comprehensive Pathway [144] and a Brief Pathway [145]. Some of the recent findings are reported below.

Service members (n = 59) who had sustained mild-moderate TBI completed the Traumatic Brain Injury Quality of Life (TBI-QOL), NSI, PCL-C, and Combat Experiences Scale within 6 months and at 1 year post-injury. Self-reported symptoms in the acute recovery phase of mild-moderate TBI were used to predict 13 outcome variables at 1 year post-injury. It was found that only PTSD, depression, and resilience were predictors of outcome 1 year post-injury and that acute PTSD and depression symptoms, followed by resilience, were the most reliable predictors of the 13 outcome variables [146]. In a related sample, the TBI-QOL scale was used in a sample of 57 service members (42 mild-moderate TBI and 15 trauma controls) at 1 and 2 years post-injury. There were no significant differences found post-injury at year 1. At year 2, the TBI sample reported worse anger, anxiety, depression, grief/loss, fatigue, emotional control, and positive affect/well-being as compared to the trauma control group (ds = 0.53–0.68). Furthermore, in the TBI group, symptom reporting worsened from year 1 to year 2 (ds = 0.23–0.51) in anger, anxiety, headaches, pain interference, cognitive complaints, self-evaluation, and social participation. The trauma control group reported stable TBI-QOL scoring throughout the study [147].

In another sample from this longitudinal study, the examination of self-reported outcome 5 years after mild-moderate TBI was investigated. Service members (n = 251; 137 mild-moderate TBI, 45 trauma controls and 69 healthy controls) completed four symptom self-report questionnaires at five or more years post-injury. The questionnaires completed were the TBI-QOL, NSI, PCL-C, and Alcohol Use Disorders Identification Test (AUDIT). The TBI group reported higher scores on the NSI and PCL-C and worse on 11 of the 14 TBI-QOL scales used as compared to the trauma control and healthy control groups. The TBI-QOL scales that identified grief/loss, cognitive complaints, post-concussion symptoms, acute stress, anger, emotional control, fatigue, anxiety, pain, headaches, and depression were the largest effects seen in the TBI group. Additionally, the TBI group had a higher number of TBI-QOL "poor outcome" scales as compared to the trauma control and healthy control groups [148].

In addition samples examining post-concussion symptoms following mild-moderate TBI from the acute/subacute recovery phase to 1 year post-injury, post-concussion symptoms were common among service members but were inconsistent over time [149]. Also, when examining the NSI in TBI and trauma control groups, many of the NSI symptoms reported at baseline resolved within 1 year for both groups. At 1 year post-injury, it was common in both groups for some baseline symptoms to persist and new symptoms to develop [150]. Expanding on these findings, post-concussion symptoms were analyzed in a sample within the first 10-years following a mild-moderate TBI (n = 521; 366 mild-moderate TBI, 86 trauma controls, and 69 healthy controls) and found not to be unique or predictive of mild-moderate TBI [151].

Access to services, service needs, and barriers to care were also investigated though the Natural History Study. In a sample of 90 service members who sustained mild-moderate TBI, a 1-h interview was conducted to collect demographics, military/civilian history, medical history, and service needs. The majority (84.4%) of these interviews occurred within 12 months post-injury. Of the service members in this study, 63.3–72.2% were receiving mental health treatment, physical rehabilitation, and care-coordination services. Specific needs identified for service members following mild-moderate TBI included memory/attention improvement, emotional concern management, and job skill development (56.7–28.9%). Many service members reported accessing their needed services (88.9–50.9%);

however, 11.1–49.1% reported that they had not. The need for services was also found to be associated with duty status, medical board hearings, poor physical and mental health, and sleep problems. Needs for services were not found to correlate to age, education, gender, number of deployments, household income, nor TBI severity. Additionally, 10.0–27.8% of this sample reported the continued need for services for problems with memory/attention, information regarding services available, and job skill improvement. More investigation must be done to identify the precise factors limiting service access; however, this study suggests that a significant number of service members may not be receiving the care/services they need or want [152].

Caregivers/Family

While concerns about the health and welfare of family caregivers of injured service members with TBI were identified as early as 2006, little attention has been paid to systematic examination of their needs over time. Families and caregivers of combat-injured service members are subject to multiple stressors and require significant support as they traverse the continuum of care. Common themes emerge regardless of severity of diagnosis. The majority of families require psychosocial support, education and information, and resource and logistical support. As the course of recovery can vary dramatically, there can be great uncertainty, contributing to stress and frustration for family members. Other concerns include difficulty accessing adequate resources in some areas of the country, the need for experienced case managers in the DoD and Department of Veterans Affairs to assist with navigation through the care system, inadequate financial resources, and gaps in resource availability [153]. See Fig. 4.

Another part of the 15-year studies was developed to examine the health and supportive care needs of caregivers of service members. This study, the "Health Related Quality of Life in Caregivers of Service Members with Military-Related Traumatic Brain Injury: TBI-CareQOL Development" (to be referred to as the Caregiver Study in this chapter), involves caregivers of service members or veterans who sustained a TBI while serving in the military after October 2001. The study's mission was also to develop a HRQOL measure for use with caregivers of military service members who have sustained a TBI called the TBI-CareQOL [154].

Fig. 4 Family stands by US Marine following his retirement ceremony. (Public Domain. Source: https://core.wazeedigital.com/video/clip/779VPI2_LCRZT496P.do?assetId=asset_16376731/clip_39537262.)

In one sample from this study examining the characteristics and perceived burden of family members, 226 caregivers were enrolled who were providing care for service members with mild to severe and penetrating TBI. Caregivers reported that they would typically help the service member in the following domains: physical, medical, self-awareness, cognitive, psychological, social interaction, communication, daily activities, and financial problems (77–99%), 7 days/week (87%), and 11–24 h/day (52%). Many caregivers rated their emotional and mental health as fair/poor (55% and 39%, respectively), and 62% reported they had suffered financial loss from caregiving. As expected, those who reported a higher burden of responsibilities while caregiving spent more time daily acting as caregiver. Additionally, those who reported a higher caregiving burden were more likely to provide physical, social, communication, and financial help to the service member with TBI (66%) and rated their own health as fair/poor both physically and mentally [155]. In that same caregiver sample, the long-term service needs, access to, and barriers to care were investigated for caregivers after the service member had transitioned home following their TBI. Caregivers retrospectively rated their healthcare needs and barriers for when the service member first moved home after injury and within the past 3 months. The most frequent service needs identified included support group access, medical system navigation, service/benefit information, and assistance providing emotional support. Only 19–36% of the caregivers who reported needing help received it after they moved home, and only 20–41% reported receiving help in the last 3 months. Additionally, 43% and 71% of caregivers reported the need for help managing their own physical and emotional needs, respectively, but only 30–38% reported receiving the help that they wanted. The barriers to receiving care included lack of awareness of services available or where to receive them, the inability to pay for services, and the concern about negative perceptions from others (31–78%). This study reinforced the need for increased care for the caregivers of injured service members [156].

By means of 90-minute focus groups, the Caregiver Study also identified key challenges that caregivers of service members with TBI face. This study encompassed nine focus groups with a total of 45 caregivers examining caregiver and service member HRQOL following TBI. The focus groups covered military and community healthcare barriers and supports (63% and 31% of the time, respectively). Barriers and supports discussed for both service members and caregivers included access to services, quality of care, and financial burden. Barriers and supports for community organizations were also discussed. Throughout the focus groups, it was emphasized that caregivers face frequent challenges within the military healthcare system. Caregivers also reported perceived health services needs that remain unmet for the service members they care for and themselves. It was concluded that increasing access to and quality of services and reducing financial burden for service members following TBI, as well as their caregivers, may lead to improved HRQOL for both the service members and their caregivers [157].

Long-Term Disease

Concerns about long-term effects of warfare expand beyond the risk associated with TBI itself. Deployment has been implicated in a number of concerns that could have longer-term implications. The Millennium Cohort Study (n = 76,924) surveyed individuals about multiple physical symptoms (MPS) at three time points. Based on self-report of ever being diagnosed with any of 24 serious and chronic physical conditions (angina, asthma, Crohn's disease, coronary heart disease, chronic bronchitis, cirrhosis, cancer, diabetes, emphysema, heart attack, hepatitis A, hepatitis B, other hepatitis, significant hearing loss, hypertension, kidney failure requiring dialysis, lupus, multiple sclerosis, neuropathy-caused reduced sensation in hands or feet, pancreatitis, rheumatoid arthritis, stroke, ulcerative colitis or proctitis, stomach/duodenal/peptic ulcer), individuals surveyed were significantly more likely to report MPS at each time point

compared with those not deployed (odds ratio [OR] and confidence interval [CI] for wave 1, 1.49 [1.47–1.52]; wave 2, 1.73 [1.69–1.78]; wave 3, 2.08 [2.03–2.12]) and those who deployed without combat (OR and CI for wave 1, 2.66 [2.59–2.74]; wave 2, 1.81 [1.75–1.87]; wave 3 = 1.68 [1.63–1.74]). This suggests that the probability of reporting MPS increases consistently over time for those deployed, regardless of combat experience [158]. Cognitive functioning and emotional functioning have been shown to be worse in those who have deployed in multiple studies [159–161], with difficulties persisting over time.

The high rates of PTSD in this population may pose additional long-term risk. Multiple studies have suggested that PTSD may be an independent risk factor for cognitive decline [162] and even early death [163]. A recent study of World Trade Center survivors has echoed that concern for individuals exposed to traumatic events outside of the military [164]. PTSD has been shown to increase coronary heart disease, thromboembolism, and atherosclerosis, especially in women [165, 166]. This has long been presumed to be related to stress, but recent evidence [167] suggests that there may be a genetic basis for the link, with 37 of 87 PTSD candidate risk genes examined also being candidate independent risk genes for cardiovascular disease. Fifteen PTSD risk genes were also independently associated with type 2 diabetes mellitus.

Concerns about alcohol abuse and dependence are also of concern, both in the context of TBI and by itself. Rates of alcohol abuse and dependence are elevated in service members after deployment [168–171]. In those with TBI, there is concern that alcohol abuse may be consequent from behavioral or mood changes related to TBI and that TBI symptoms may be exacerbated or recovery may be compromised in those with both conditions [172–176]. This is in addition to the general physical, behavioral, and emotional concerns related to long-term alcohol abuse [177–180].

McKee and colleagues [181] have described a progressive tauopathy that they purport occurs as a consequence of repetitive mTBI. The diagnosis is based on a number of postmortem studies that they have conducted, e.g., [182–186]. They have used the term "chronic traumatic encephalopathy" (CTE) (first coined by Miller [187]) to describe the condition.

In 2013, McKee and colleagues described a spectrum of p-tau pathology in 68 males with a history of exposure to repetitive brain trauma with neuropathological evidence of CTE, ranging in age from 17 to 98 years (mean 59.5 years). Based on these findings, the group drafted proposed preliminary criteria for the neuropathological diagnosis of CTE: (1) perivascular foci of p-tau immunoreactive neurofibrillary tangles (NFTs) and astrocytic tangles (ATs) in the neocortex; (2) irregular distribution of p-tau immunoreactive NFTs and ATs at the depths of cerebral sulci; (3) NFTs in the cerebral cortex located preferentially in the superficial layers (often most pronounced in temporal cortex); and (4) supportive, non-diagnostic features (clusters of subpial ATs in the cerebral cortex, most pronounced at the sulcal depths) [181, 188].

There remain many questions about the diagnosis, however. A recent paper [189] found it difficult to exactly utilize the staging scheme outlined by McKee and colleagues. Additionally, the authors found that a significant proportion (35%) of the adult population greater than 60 years old, who undergo a medicolegal autopsy, have at least minimal CTE-like changes. These changes were often, but not exclusively, associated with histories of head injury and/or substance abuse. They further questioned whether CTE-like changes represent early features of a neurodegenerative disease, as the absence of CTE-like changes at sites of contusion argued against that likelihood. Other researchers have expressed similar concerns about an increasingly generally accepted association without sufficient evidence [190, 191]. Castellani and colleagues [192] concluded in one recent commentary that the association between the history of concussion and findings of p-tau at autopsy is unclear. They go on to state that in the available studies published, concussions and subconcussive head trauma exposure are poorly defined and the clinical features reported in CTE are not at present distinguishable from other disorders. Despite the

concerns about the limitations of these studies, they remain an area of active investigation in the DoD [184, 193, 194].

Models of Care for Military Service Members and Veterans Coping with the Chronic Effects of TBI

Though overt hostilities in the Middle East have decreased substantially in recent years, the ongoing care of patients affected by TBI remains a priority for those entrusted to care for injured US service members. As previously described, DoD estimates show that new TBI diagnoses remain threefold higher now than prior to OEF/OIF/OND, with 84% of injuries occurring in the nondeployed setting [195]. With large numbers of patients with TBI being managed in the DoD and Department of Veterans Affairs healthcare systems, research into optimal Models of Care remains an important issue as both organizations transition to become providers for chronic health conditions associated with a history of TBI. What emerges is the recognition that, even with a majority of those affected making a full recovery, the management of those with persistent, often numerous, symptoms related to TBI requires an understanding of the interweaving of these clinical symptoms and an appreciation for how a system of integrated care provided by many clinical specialties is often needed for appropriate care.

An integrated multidisciplinary team of experts, with care that is organized and coordinated and actively managed by nurse and/or social work case managers embedded in this team, must be prepared to manage a multitude of symptoms and presentations: musculoskeletal pain and headache, dizziness, sleep disturbances, and emotional concerns [196]. The co-occurrence of behavioral health disorders such as depression, PTSD, and substance use disorders, and the stigma associated with psychiatric diagnoses and behavioral health treatment(s) must also be acknowledged by this interdisciplinary team. Studies to support the benefits of an intensive outpatient or residential treatment program for chronic PTSD and TBI have shown that reducing PTSD symptoms is strongly associated with a reduction in post-concussive symptoms following this treatment [197, 198]. This supports the importance of an interdisciplinary team that should also include behavioral health specialists in every step of the TBI care continuum.

In the civilian sector over the past several years, responding to often expensive, inefficient, and fragmented care that did not consider the patient central to the treatment program, some leading health systems have developed the concept of the "Integrated Practice Unit" (IPU). In an October 2013 Harvard Business Review article, the IPU concept was described as a "strategy that will fix health care" [199]. Organized around both the patient and the need, it reduces the stovepiped organization of care by specialty departments and discrete services by instead organizing care around the patient's medical condition and symptoms. In an IPU, a dedicated team made up of both clinical and nonclinical personnel provide the full spectrum of care for the patient's condition, and this approach has been demonstrated to reduce time away from work, speed up recovery time, reduce inefficiencies and cost, and ultimately provide a more satisfying patient experience [199]:

> IPUs treat not only a disease but also the related conditions, complications, and circumstances that commonly occur along with it—such as kidney and eye disorders for patients with diabetes, or palliative care for those with metastatic cancer. IPUs not only provide treatment but also assume responsibility for engaging patients and their families in care—for instance, by providing education and counseling, encouraging adherence to treatment and prevention protocols, and supporting needed behavioral changes such as (substance abuse) cessation or weight loss. In an IPU, personnel work together regularly as a team toward a common goal: maximizing the patient's overall outcomes as efficiently as possible. They are expert in the condition, know and trust one another, and coordinate easily to minimize wasted time and resources. They meet frequently, formally and informally, and review data on their own performance. Armed with those data, they work to improve care—by establishing new protocols and devising better or more efficient ways to engage patients, including group visits…(and) collocating IPU members to help with facilitating communication, collaboration, and efficiency for patients [199].

Both the VHA and the MHS have embraced the general concept of the IPU using versions of interdisciplinary teams in the care of those dealing with both the acute and chronic effects of trauma, to include TBI. Using a tiered approach based on demand, local resources, and the benefits of a nationwide health and trauma care system continuum and logistical support, TBI programs have gained significant attention and resources in the past 10 years. The MHS and VHA have gone to great lengths in recent years to research and develop these integrated programs, developing promising and best practices along the way for the evaluation and treatment of those enduring the chronic effects of TBI.

In the DoD MHS, tiered echelons of care are employed in both the Army and Navy medical systems. Both are similar, with essentially four categories of TBI care offered at military treatment facilities (MTF) based on size, TBI severity and complexity of patients seen, and specialty care available. In the Navy, the system is tiered into Categories 1a, 1b, 2, 3, and 4. Category1a facilities provide both inpatient and outpatient TBI care and rehabilitation for the full spectrum of TBI severity (mild, moderate, severe, and penetrating TBI). Category 1b MTFs provide inpatient and outpatient care for the full spectrum of TBI severity, with only outpatient rehabilitation capability. Category 2 facilities provide inpatient and outpatient care for mild and moderate TBI, with outpatient rehabilitation capability, but have the capability to refer for higher tiered care at another MTF or within the local civilian network. Category 3 hospitals provide outpatient TBI care for mild and moderate TBI with outpatient rehabilitation and again have the capability to refer for higher intensity care at another MTF or within the local civilian network. Category 4 MTFs manage TBI in the primary care setting and are not required to have dedicated TBI assets, such as a TBI program manager, but must maintain TBI clinical coordinators, usually case managers working with clinicians to oversee TBI assessment, treatment, and care coordination either locally or in the MHS TBI care network. Category 1–3 MTFs also must have TBI program managers; in all cases the TBI program, managers and TBI clinical coordinators are assigned by the MTF commanding officer. One Navy category 1a MTF describes its approach to managing those with suspected TBI using a "multidisciplinary model" that includes neurology, occupational therapy, neuropsychology, mental health, cognitive behavioral therapy, anger management, family education, and coping skills education [21] to successfully manage their TBI patients' acute and persistent clinical needs. In contrast, a smaller Navy community MTF (Category 4) has a single TBI specialist who elicits the support of a limited number of local MTF and community-based assets to care for those with mTBI. For more severe TBI or for those with persistent symptoms exceeding local capability, the clinician works with the care coordinator/case manager to arrange referral to civilian services locally if available, a higher category of military care either locally or through the military network, or more intensive care through the VHA network, with whom they have a very good relationship and mutually support.

Similar to the Navy's system of TBI care, the Army Medical Department (AMEDD) has established a care network centered on MTFs that provide tiered care for service members with mild, moderate, severe, or penetrating TBIs. See Fig. 5. The AMEDD has established standards of care for soldiers with TBI to ensure that services, physical facilities, and staffing levels are consistent across the Army MTFs based on the level of care provided at the facility. As with the Navy Medical Department, the Army program is based on the scope and depth of care offered and is divided into four categories – 1, 2, 3, and 4. Category 1 facilities provide inpatient and outpatient medical and rehabilitative care for the full spectrum of TBI severity (mild, moderate, severe, and penetrating). Category 2 MTFs provide inpatient and outpatient medical and rehabilitative care for mild and moderate TBI. Category 3 facilities provide outpatient medical and rehabilitative care for service members with mild and mild-moderate TBI. Category 4 sites provide outpatient medical care for service members with mTBI and refer to the local network or higher echelons of military care for

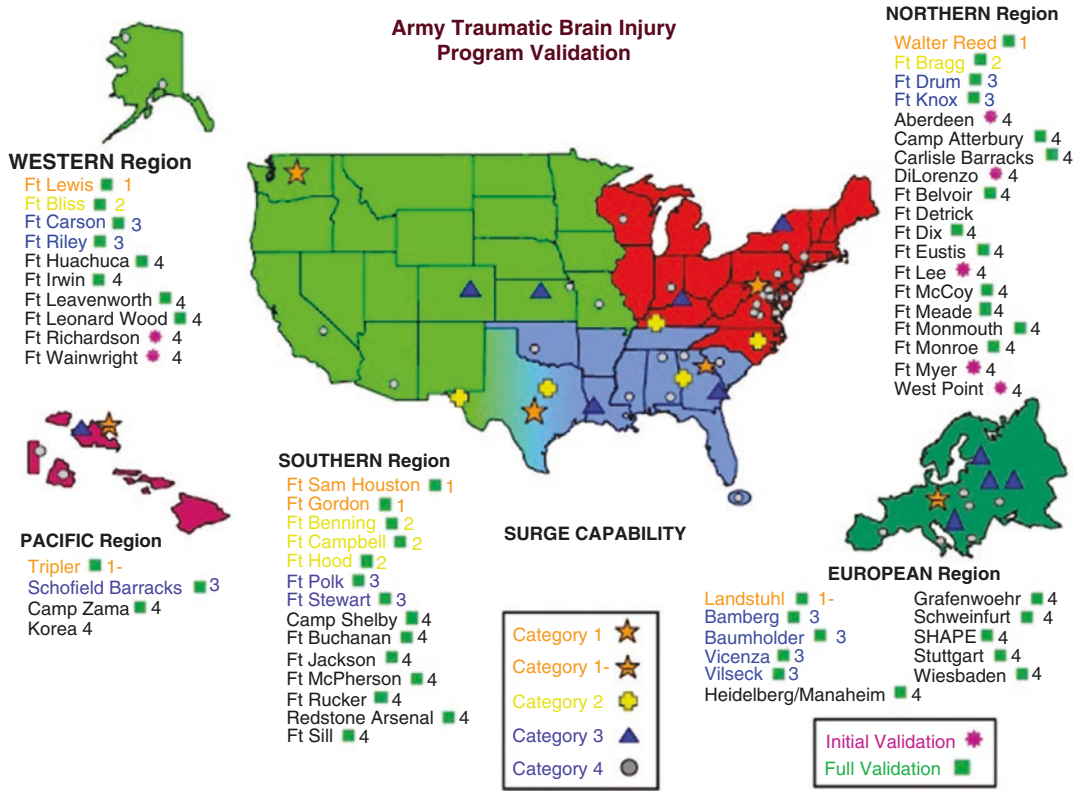

Fig. 5 Army TBI Program Validation sites as of January 2011. (Public Domain. Source: http://armymedicine.mil/Documents/R2D-TBI_Program_Validation_Fact_Sheet.pdf)

additional services as needed [200]. An example of an Army Category 1 site is an Army Regional Medical Center augmented with teams consisting of 8 to 17 personnel, including a TBI inpatient program director, physical medicine and rehabilitation physician, neurologist, nurse practitioner or physician assistant, neuropsychologist, physical therapist, occupational therapist, speech language pathologist, clinical nurse specialist, social worker, rehabilitation nurse, pharmacist, recreation therapist, counseling psychologist, psychiatrist, TBI program administrator, and TBI program liaison. A smaller Army outpatient MTF may be Category 2 or 3 and is staffed with "detection and initial treatment teams," but may have augmented teams at high troop density sites. These teams, which consist of 6–14 personnel, are typically made up of a primary care provider, behavioral health provider, nurse case manager, licensed practical nurse, program liaison, and administrative staff. Additionally, rehabilitation teams can augment sites with high numbers of patients with TBI and typically consist of 5–8 personnel, such as a physical medicine and rehabilitation physician, neurologist, psychiatrist, speech language pathologist, physical therapist, physical therapist assistant, occupational therapist, and occupational therapist assistant [200].

An additional and unique asset added recently to the MHS portfolio of TBI care capability is the National Intrepid Center of Excellence (NICoE), gifted to the MHS by the American people through the Intrepid Fallen Heroes Fund as a clinical research institute dedicated to the evaluation, treatment, and research of those affected by the comorbid states of TBI and psychological health concerns such as PTSD. Established in late 2010 on the campus of what was to soon become the Walter Reed National Military

Fig. 6 National Intrepid Center of Excellence, Walter Reed National Military Medical Center. (Public Domain. Source: https://core.wazeedigital.com/video/clip/779S1Z8_GOIPJL5S1.do?keywords=national%2Cintrepid%2Ccenter%2Cof%2Cexcellence&fieldTermQueries=itemType:clip)

Medical Center (WRNMMC) in Bethesda, Maryland, the NICoE and, more recently, a complementary network of similarly proffered facilities located around the country called Intrepid Spirit Centers has gained an important place within the MHS's TBI continuum of care. Based on the premise that TBI rarely occurs without significant and confounding comorbidities, staff at the NICoE use an aggressive interdisciplinary approach similar to those described above, placing a heavy emphasis on complementary and integrative ("alternative") medicine, such as mind-body-wellness/meditation, animal-assisted therapy, yoga, art/dance/movement/creative writing therapy, acupuncture, and other complementary techniques, collocated in one building which itself is an important healing space [201]. Using this approach and managing TBI in both inpatient and long-term, outpatient care, as well as shorter but more intensive outpatient programs, the NICoE and the Intrepid Spirit Centers have defined a category of care not well encapsulated in traditional Army or Navy medicine dogma, but which highlights a paradigm shift in disease management from a stove-piped, diagnosis-based approach to a holistic, integrative, and patient-centered approach. The success and durability of this type of system is being validated with small but growing evidence indicating that dramatic improvements seen at the time of treatment in patients with comorbid TBI and psychological health symptoms persist long after the service member has been through these intensive programs. Additionally, service member retention, functional status, healthcare, and pharmaceutical utilization are closely followed as metrics for the success of such programs as well. See Figs. 6, 7, 8, and 9.

Along the trauma continuum of care, including more severe TBI injuries, the MHS works closely with the VHA and its excellent network of polytrauma medical centers that comprise the Polytrauma System of Care (PSC). Once the acute phase of a trauma is stabilized and

Fig. 7 Central Park, National Intrepid Center of Excellence, Walter Reed National Military Medical Center. (Public Domain. Source: https://core.wazeedigital.com/video/clip/75M237107_x01.do?assetId=asset_16376701/clip_35593183)

Fig. 8 Art Therapy at the National Intrepid Center of Excellence, Walter Reed National Military Medical Center. (Public Domain. Source: https://core.wazeedigital.com/video/clip/779P2O7_XJPABN82K.do?assetId=asset_16376710/clip_39092426)

longer-term needs are assessed, some active duty patients make their way to the VHA system for specialized care and rehabilitation. For some, they remain for long periods of time. For others, once rehabilitation plans been established and initiated, the service member may return to the MHS for more targeted outpatient therapy as well as medical and administrative disposition. Both veterans and active duty service members have access to this integrated nationwide system of care. With the VHA's development of the national deployment health clinic care model and partnering with PSC, the current system is designed to provide access to lifelong rehabilitation services for patients recovering from polytrauma and TBI [202]. See Figs. 10 and 11.

Similar to the MHS, the VHA's PSC has four categories to its tiered system of care. PRCs are the first component, of which there are five across the country. PRCs provide acute medical and rehabilitation care, perform research, and engage patients and their families in education related to polytrauma and TBI [203]. Much like the MHS's integrated teams, clinical care at the PRC is provided by an interdisciplinary team that includes rehabilitation specialists and medical consultants with expertise in the treatment of physical, emotional, behavioral, and psychological problems.

Fig. 9 Map of the current and upcoming Intrepid Spirit Centers. (Courtesy of National Intrepid Center of Excellence, Walter Reed National Military Medical Center)

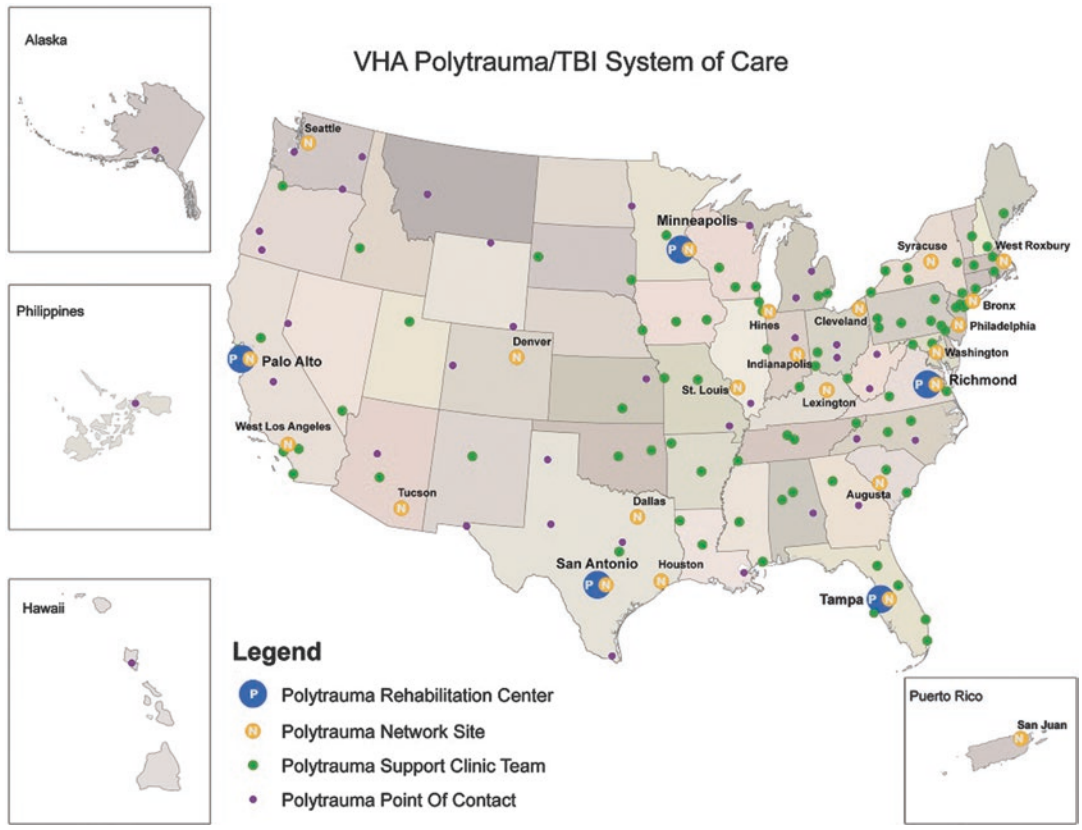

Fig. 10 VHA Polytrauma/TBI System of Care Locations. (Public Domain. Source: http://www.polytrauma.va.gov/system-of-care/care-facilities/)

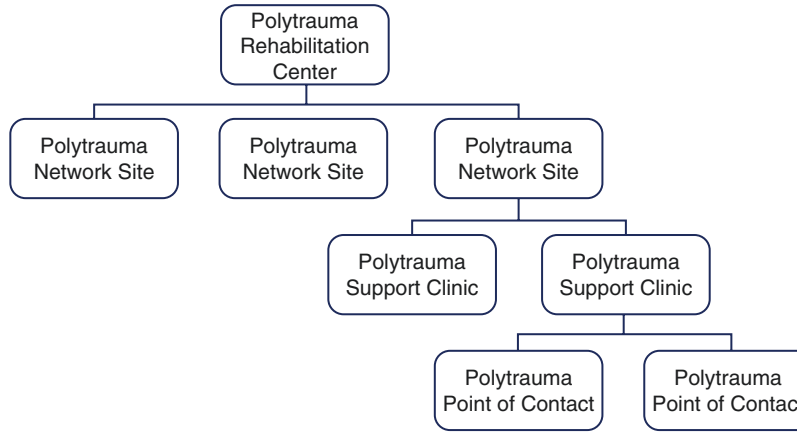

Fig. 11 VHA Polytrauma/TBI System of Care Organizational Chart. (Public Domain. Source: http://www.polytrauma.va.gov/system-of-care/index.asp.)

Being mostly inpatient programs, PRCs care for both the active duty service member and veteran with the full spectrum of injuries, to include mild, moderate, severe, and penetrating TBI, for long periods of time, including lifelong care in the case of severe disability with limited recovery [203]. There are 21 sites in the second component in the VHA's tiered system, designated in 2005 as Polytrauma Network Sites (PNSs). They are located across the VHA's 21 regional veterans integrated service networks (VISNs). Much like the MHS's Category 2 sites, PNSs provide both inpatient and outpatient services as well as post-acute rehabilitation services such as vocational rehabilitation. Aggressive case management remains a vital component to the success of these programs, ensuring access to care both in the VHA and civilian networks in order to meet patients' and families' needs. Community reintegration is the outcome most sought for all, including those with TBI [203]. The polytrauma support clinical team (PSCT) makes up the third component of the PSC, providing specialized rehabilitation and clinical support services close to the homes of both veterans and active duty service members referred to them. Responsible for providing treatment plans, general and specialty follow-up care, and making adjustments to care plans as circumstances change, PSCTs are interdisciplinary teams that also provide referrals to higher echelons of care within the VHA or civilian network as the need dictates. Since all VHA medical centers have specific polytrauma/TBI points of contact and are responsible for managing consultations for these patients, a transition of care from lower to higher intensity is made more seamless [203, 204].

The MHS and the VHA have gone to great lengths to standardize care across their respective TBI continuums, with less dependence on local expertise and resources and decreased regional variations in the quality and success of this system of care for chronic TBI. The most important aspect of this new way of thinking is a national-level effort of "managing" this pathway of care for TBI, to include the important relationship between the VHA and MHS. In 2014, the DoD Assistant Secretary of Defense for Health Affairs released a policy memo describing the expectation of achieving a national TBI Pathway of Care, to be overseen by DVBIC [205]. The TBI Pathway of Care currently being realized is leveraging all the important aspects of the care continuum just described into a national network of TBI treatment facilities to ensure that the right patient receives the right care at the right time and right place. With voting and non-voting representatives from all military services, the Defense Health Agency, DVBIC, the Uniformed Services University of the Health Sciences, the NICoE, and the VHA, the TBI Advisory Council (TAC), newly chartered in 2015, is helping define the best practices and ideal way forward for managing this very important health issue.

Conclusion

Whether a TBI results in long-term consequences depends on multiple factors, including the severity of the injury, the context and mechanism of the injury, premorbid characteristics of the injured individual, environmental factors including stressors, and comorbid health conditions, especially mood changes, stress symptoms, pain, and extracranial injuries. Recent efforts in the DoD and VHA have been to treat the spectrum of health conditions in a holistic way. This is especially important as the exact etiology of symptoms is not always clear, and some symptoms can mimic one another or even conditions that are part of normal life (e.g., headache, sleep problems, etc.). Furthermore, there are a number of deployment-related health conditions outside of TBI that can cause longer-term health problems. Vigilance is indicated, both from a clinical and research standpoint. It is crucial that we continue to study long-term effects of injury on the patient and family, with the goals of enhancing services, improving treatments, and increasing long-term quality of life.

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Rehabilitation Following TBI

Mel B. Glenn and Shirley L. Shih

Introduction

Traumatic brain injury (TBI) can cause a wide variety of motor, cognitive, behavioral, emotional, and medical problems. Rehabilitation following TBI is, therefore, a complex endeavor requiring a team approach involving physicians, nurses, neuropsychologists, psychotherapists (e.g., psychologists, social workers, or mental health counselors), speech and language pathologists (SLPs), occupational therapists (OTs), physical therapists (PTs), vocational counselors, recreational therapists, and case managers. This entails the need for strong communication among team members and considerable flexibility on the part of the team. Therapists often have to take roles that may not be required in other settings. For instance, physical therapists will treat the physical mobility issues, including community navigation skills and safety. However, they have to be tuned into how cognitive dysfunction will affect mobility and how best to address it. They will also be confronted with the behavioral disorders that are prominent among people with TBI: disinhibited behavior, including aggression, but also apathy. OTs will work on activities of daily living (ADLs) and upper limb mobility, but will do so in the context of cognitive disability as well. Home and community skills, such as balancing a checkbook, meal preparation, and shopping, will take on greater importance in the rehabilitation of people with TBI because of the cognitive dimension. OTs, too, will have to treat behavioral disorders. SLPs will treat not only language, swallowing, and speech deficits among people with TBI but also cognitively based communication deficits. They will also treat problems with memory, attention, and executive skills and may overlap with OTs in the areas of home and community skills, such as scheduling and money management. Of course, SLPs will have to know how to manage behavioral issues as well. Nurses and the nurses' aides will have to deal with every dimension: medical, mobility, cognitive, and behavioral. Most TBI programs have neuropsychologists and/or behavioral psychologists who do neuropsychological assessments; guide the team with respect to cognitive, emotional, and behavioral treatments; and sometimes do counseling. The neuropsychologist has to apply his or her understanding of the cognitive and behavioral issues to pharmacology, mobility, ADLs, and home and community

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rehabilitation. Although important in all areas of rehabilitation, in rehabilitation following TBI, it is crucial that the physician listens to all team members, as well as family members. The physician is not going to learn all the details of what a patient is doing and saying with respect to emotional, behavioral, and cognitive status directly from the patient. The therapy and nursing staff, as well as family, will be the ones who observe the intricacies of the patient's inattention, disinhibition, and apathy and hear about the patient's despairing thoughts and so forth. At the same time, if the physician starts the patient on a medication for a cognitive, emotional, or behavioral issue, he or she will get a more complete perspective on the patient's response by hearing from other team members.

When it comes to treating physical issues, it is important that team members communicate their findings and concerns to one another. Disorders of muscle tone can change from moment to moment and differ with position. The therapist may see these changes manifested in different ways than will the physician. If the physician is going to intervene with medications or procedures, it is important that he or she understands the functional context in which the problem occurs. Again, the other team members' input will give the physician the information needed to make decisions about whether to try medications or whether or not they have been beneficial.

Medical problems, too, will affect the patient in every setting. It is important for the therapy staff to be aware of the medical status of the patient, which may change the person's physical, cognitive, and behavioral status. Therapy staff or family may be the first to see a change in a patient's status that will alert the physician to the possibility of medical issues or side effects of medications. Medical issues are covered in other chapters in this book.

Inpatient rehabilitation following TBI results in improved outcomes. Inpatient multidisciplinary rehabilitation beginning 4 weeks or less from the time of injury improved independence in mobility and ADLs in patients with severe TBI compared to a control group of inpatients in nonspecialty hospitals. Caregiver distress decreased more in the intervention group as well [1, 2]. Salazar and colleagues [3] did a randomized controlled trial (RCT) of inpatient cognitive rehabilitation vs. education, advice, and weekly telephone follow-up in a population of independently ambulating military personnel with TBI who had a Glasgow Coma Scale (GCS) score of 13 or less at the time of injury and a current Rancho Los Amigos Levels of Cognitive Function Scale (RLAS) score of 7. They found no difference in gainful employment or fitness to return to military duty nor in cognitive and behavioral/emotional performance between groups. However, a post hoc analysis found that among the more severely affected (loss of consciousness [LOC] greater than 1 h), the inpatient rehabilitation group had a better rate of return to duty [3]. The appropriateness of this high-functioning group for inpatient rehabilitation has been questioned [4]. RCTs have found that additional therapies [5] or the presence of an experienced brain injury professional on the rehabilitation team [2, 6] results in more rapid gains, but does not seem to change the ultimate outcome [2]. The vast majority of patients who attend inpatient rehabilitation programs following acute care are discharged to home. Older age, living alone before the injury, and lower admission FIM (Uniform Data System for Medical Rehabilitation, a division of UB Foundation Activities, Amherst, NY, USA) instrument scores in bladder management, bed-chair-wheelchair transfers, and comprehension are associated with discharge to skilled nursing facilities and other institutions [7]. Lower discharge FIM scores in bladder management, locomotion, and socialization are also associated with institutional discharge [8].

Controlled studies have also found post-inpatient residential, outpatient, and home rehabilitation to be effective for people with TBI. A single-blind RCT of community-based team rehabilitation for patients with severe TBI 3 months to 20 years after injury (mean 27 weeks) demonstrated improved mobility, ADLs, and participation-level skills (Brain Injury Community Rehabilitation Outcome [BICRO]-39 scales) in 40% of patients compared to 27% of the controls given only written information [2, 9]. In a single-blind RCT of a home-based multidisciplinary rehabilitation program for patients with severe

TBI, improved mobility and ADLs were seen, as well as participation-level outcomes on the BICRO-39 in the intervention group [2, 10]. An RCT comparing holistic, integrated cognitive, interpersonal, and functional outpatient rehabilitation with individual discipline-specific outpatient therapies for patients with TBI reported significantly greater gains in community functioning, quality of life, and self-efficacy for management of symptoms in the holistic rehabilitation condition [11]. A prospective cohort study comparing a residential rehabilitation program with a 3-month waiting list control group and 1-year follow-up found gains in independent living, societal participation, emotional well-being, and quality of life in the rehabilitation group of patients with chronic acquired brain injury (ABI) (67% TBI) and psychosocial problems affecting their ability to function in society [12]. A 3-year follow-up found the gains to be maintained [13]. Malec and Kean [14] analyzed a large database (N = 3087) from post-inpatient programs and found gains in the Mayo-Portland Adaptability Inventory (MPAI)-4 in residential and outpatient community-based rehabilitation compared with maintenance supported living programs. Participants were a mean of 587 days (SD = 1789 days) post-injury.

Motor Disorders

Definitions

There are several motor disorders commonly affecting people with TBI. Weakness is probably the most common disorder and can be addressed with strengthening exercises. This has not been studied in detail in people with TBI. Weakness is often seen with other motor disorders. These disorders are often seen together in various combinations, so it is best to start with definitions and descriptions.

Signs of ataxia include intention tremor and postural tremor. These are perhaps the most difficult of all motor disorders to treat. Although buspirone may have some modest effects on ataxia [15], there are no medications that have been shown to have clear clinically significant benefit. Weighted extremities can help at times, but the effect is small. Velcro wrist or ankle weights or ankle-foot orthoses with double metal uprights can be used. The only approach that is always worth trying is repetitive therapeutic exercise (e.g., reaching for a target or picking up a cup of water and bringing it to the mouth or, for the lower limbs, walking with as narrow a base as possible). Some patients will make slow gains with thousands of repetitions of the same activity. Others will be left frustrated by the lack of progress. Goals should be set that are achievable in order to minimize frustration.

Spasticity and rigidity are both disorders of muscle tone. Muscle tone is reflexive resistance to passive stretching of muscle. Spasticity is a manifestation of hyperactive stretch reflexes, one aspect of the upper motor neuron syndrome. It is characterized by a velocity-dependent increase in muscle tone (hypertonia) with a catch and release (including the specific "clasp knife" phenomenon), hyperactive deep tendon reflexes, and, at times, clonus. It is often seen with other aspects of the upper motor neuron syndrome: weakness, impaired timing, and poor coordination [16, 17]. It is important to treat spasticity in instances where it causes functional limitations; interferes with daily tasks, such as dressing, hygiene, or proper positioning in a wheelchair; or generates a significant degree of pain. Spasticity is not always detrimental and can sometimes provide functional benefit. In some cases, lower extremity spasticity may not impact mobility outcomes [18], and increased muscle tone in the hip and knee extensors may allow a person to bear weight on an otherwise weak extremity. Spasticity of the elbow flexors can make it possible for someone to carry a purse or shopping bag on the forearm. Increased tone in the finger flexors can allow a person to hold objects in the hand.

Rigidity is another form of hypertonia. In this case, the increase in muscle tone is not velocity dependent, and it is consistent throughout the available range of motion [16, 19]. Parkinsonian rigidity with cogwheeling can occur after TBI. In addition, gegenhalten or paratonia, in which there is a feeling of voluntary resistance [20, 21], can be seen as well.

Dystonia is also quite common. Dystonia occurs when involuntary muscle contractions result in intermittent or persistent posturing [16, 19, 22, 23]. Dystonia is not necessarily a hypertonia; that is, it may or may not be elicited by a muscle stretch. It can be seen spontaneously or can be elicited by a sensory stimulus, such as touch, perturbation, or even a loud noise. Technically, decerebrate and decorticate rigidity are dystonias. Spasticity can result in dystonic posturing. There is probably more than one neurophysiologic etiology.

Although more commonly seen in spinal cord disorders, involuntary flexor or extensor spasms of the limbs can be seen after TBI. These are sudden jerking movements that are manifestations of hyperactive cutaneous or soft tissue reflexes. Synergies and, less commonly, postural reflexes can be seen after TBI as well. These are obligate patterns of movement initiated by active (synergies and postural reflexes) or passive (postural reflexes) motion of a limb or, in the case of postural reflexes, the head and neck or trunk. The individual is unable to move joints in isolation [16, 24].

Treatment

The mainstay of treatment of the upper motor neuron syndrome for all of these entities is therapeutic exercise and functional training done by physical and occupational therapists, including sustained stretching of muscles and soft tissues. Electromyographic (EMG) biofeedback can be helpful to facilitate isolation of the muscles that are most problematic, though the literature on its efficacy is limited [25, 26]. Although thus far the best evidence for its efficacy has been in subjects with stroke, constraint-induced movement therapy (CIMT) [27] or a modification of the full therapy [28, 29] can be done for the hemiplegic individual with TBI who is capable of complying with the rigorous schedule [30]. It is most frequently used to facilitate movement of a partially impaired upper limb. In full CIMT, the patient receives therapy for the more impaired limb 6 h a day, combining repetitive task practice with adaptive task practice. The latter involves practice of components of the task and eventually the entire sequence, with a gradual increase in task difficulty. The stronger limb is restrained with a mitt or other devices for 90% of waking hours, forcing the patient to use the partially impaired extremity. The patient keeps a log of his/her activities as a check on compliance and to reinforce the behaviors. It has been successful in the subacute and chronic settings where it has been shown to improve upper limb use following stroke [27, 31]. However, limb restraint in the acute rehabilitation setting has been unsuccessful and even detrimental with a more intensive therapy group [32]. CIMT is based on the hypothesis that people with hemiplegia make limited gains in the use of the impaired upper limb because of "learned disuse." This theory suggests that in the early days of rehabilitation, people with hemiparesis who do not make rapid gains will limit the use of the impaired extremity and instead emphasize compensation using the stronger extremity because of the frustration and lack of positive reinforcement received from limited success. Thus, the full potential for recovery is not reached [33].

The initial approach to problems with spasticity includes treating provocative nociceptive influences, in particular, skin, bladder, and bowel problems. This decreases the noxious input into the central nervous system (CNS) that facilitates excitation of motor neurons [16, 20]. Sustained stretch through range of motion exercises is also key and generally needs to be done at least daily if there is a significant amount of spasticity. Positioning is also crucial for limiting spasticity. For instance, if, when sitting in a wheelchair, a person is tending to slide out due to hip and knee extensor tone, a tilt-in-space wheelchair will take advantage of gravity to hold the hips in flexion. A seatbelt across the pelvis will help to keep the hips at 90 degrees. If the toes are held down with toe loops, the knees will remain flexed. Maintaining this position will stretch the hip and knee extensors as well as the ankle plantar flexors, and the spasticity will decrease [34].

There are also a number of physical modalities that physical and occupational therapists use

to treat spasticity that tend to work in the short term and can be used before stretching or other therapeutic exercises. Warmth can decrease muscle tone. Cold generally increases spasticity in the short run, but after 15 or 20 min, it will decrease the tone [35]. Ultrasound is a deep heating method. If the elastic portions of the tendon and muscle are warmed, they become more flexible, and then more stretch can take place before the muscle spindle gets stretched. Electrical stimulation can be used, both in the antagonist and the agonist muscles. In the antagonist muscle, reciprocal inhibition is leveraged to inhibit the muscle tone in the agonist muscle. In the targeted agonist muscle group, electrical stimulation over a period of time can deplete acetylcholine from the neuromuscular junction, thus fatiguing the spastic muscle [35]. However, small studies investigating the coupling of electrical stimulation to splinting do not appear to demonstrate added benefit compared to stretching and splinting alone [36]. Low-frequency generalized vibration can also be used to decrease spasticity [37].

Casting and orthotics can decrease muscle tone, though casting tends to be more effective [35, 38, 39]. If well applied, the soft tissues are held in a position for a sustained period of time, thus reducing muscle tone. However, a cast or orthotic that does not hold a joint well and allows for some movement will often provoke an increase in tone by acting as a noxious stimulus to the skin.

Medications can be helpful, though are used less frequently in people with brain injury than with spinal cord injury because many of them have deleterious cognitive side effects. Diazepam and other benzodiazepines cause sedation, as well as attention and memory problems that may persist following withdrawal [40, 41]. They are generally to be avoided except in situations in which the hypertonia, dystonia, or muscle spasms are so severe as to be painful or otherwise disruptive, thus becoming a major distraction to the patient, and in which other approaches have either failed or are relatively contraindicated. They are not FDA approved for this use ("off-label"). Baclofen can be useful for treating spasticity and muscle spasms but has been found to impair memory in animal experiments [42, 43]. There is little evidence for its efficacy in people with spasticity caused by cerebral lesions [35], although anecdotally, individual clinicians have found it helpful at times. Cyproheptadine has been used to treat spasticity, but studies in people with spasticity resulting from cerebral lesions are extremely limited. Its sedating effect can be a major drawback [35]. Clonidine was used more frequently in the past ("off-label") but has largely been replaced by tizanidine, which is also a central alpha-2 agonist that decreases spasticity, but with less effect on blood pressure. However, side effects, in particular sedation, often limit its use. Because of data suggesting that clonidine can inhibit recovery from CNS lesions, tizanidine is suspect as well [35]. Tizanidine can also cause elevated liver function tests [35]. As an "off-label" use, gabapentin has been shown to be effective for treating spasticity in persons with multiple sclerosis at doses of about 2700 mg a day [44], though individual dosing varies. Gabapentin can be sedating, but if titrated slowly, many patients accommodate to this effect. It is otherwise generally free of adverse cognitive effects [44–46]. Dantrolene sodium is generally thought to be without deleterious cognitive effects, though studies in animals have shown an adverse effect on memory [47, 48]. Whereas the drugs previously mentioned work in the CNS at the reflex level, dantrolene works at the muscle itself by inhibiting the release of calcium from the sarcoplasmic reticulum. Hepatotoxicity is a serious potential problem, so liver function tests must be followed. However, efficacy appears to be optimal at doses of 200 mg daily or less, and at that dose the risk of hepatotoxicity is small. Dantrolene does tend to cause weakness in the non-spastic muscles [35]. Because it acts peripherally, any muscle can be affected by it. Although generally not a problem if the muscle is unused or is strong, in areas where the person is weak, dantrolene may tip them over the edge into weakness that affects function, including muscles involved in swallowing and speech. Compliance with oral anti-spasticity agents has been found to be relatively poor in the TBI population, particularly among younger individuals [49].

When cogwheel rigidity is present, the same dopaminergic agents that are used in Parkinson's disease can be tried ("off-label"), although this needs further study. Dystonia is very difficult to treat, and in patients with TBI, the pharmacologic approaches are "off-label." Anticholinergic agents can be used, though they are generally of limited benefit [50]. They can adversely affect memory and attention [51, 52]. Benzodiazepines can be very effective, but as noted above, they can cause sedation and cognitive impairment [40, 41].

Chemical denervation using botulinum toxin, phenol, or even alcohol will often provide a better risk-to-benefit ratio because of the lack of cognitive side effects. This is particularly the case when hypertonia or dystonia is focal rather than generalized or in situations in which the need for intervention is limited to a small number of areas. Chemical neurolysis with phenol destroys axons, but weakness is not a common complication if used discretely. There is a very variable duration of action, from weeks to years. It often lasts longer than 6 months, which is in some ways an advantage and in other ways a disadvantage over botulinum toxin. It is most useful when the patient cannot or does not want to return frequently for injections, when the limit for the quantity of botulinum toxin has been reached and there are still areas in need of treatment, or when botulinum toxin is not effective. It can also be used as an adjunct to botulinum toxin. When only motor branches are blocked, then the common side effects are transient pain and occasionally swelling at the injection site, depending on how much is used and which muscles are injected. If mixed sensorimotor blocks are done, some patients (10–32%) will get dysesthesias in the sensory distribution of the nerve. This is usually a mild "pins and needles" sensation that lasts for 2 or 3 weeks and then resolves. Occasionally, these painful sensations need treatment with transcutaneous electrical nerve stimulation, a tricyclic antidepressant ("off-label"), or other medications until they have run their course. Rarely dysesthesias continue for longer periods of time. In such cases, reinjection with phenol at the same site will usually resolve the pain. The best approach to this issue is to prevent the problem entirely by doing motor branch blocks or injecting peripheral nerves that are largely motor, such as the thoracodorsal or obturator nerves. Usually, a motor branch block is sufficient to reduce spasticity, but mixed sensorimotor blocks are at times necessary to get a better result. Goals of treatment should be clear before injections are done [21, 53]. The use of phenol to treat hypertonia or dystonia is not FDA approved.

Botulinum toxin inhibits release of acetylcholine at the neuromuscular junction. There are several serotypes, but the only ones that are commercially available are botulinum toxins A and B. Within each serotype, there are preparations that differ according to the company that produced the toxin. The duration of effect (generally 2–6 months) is usually shorter than with a phenol block. This makes it a better choice when there is a concern that the procedure might adversely affect a person's function. There is a limit to how much botulinum toxin can be used in any given therapeutic period (approximately 3 months). If there are several muscle groups to cover, especially when bilateral procedures are necessary, it may not be possible to treat them all with botulinum toxin. There is a limit to how much phenol can be injected in a given day, but over a period of a few weeks, more can be used [53]. Botulinum toxin is relatively free of side effects and complications, although dysphagia and respiratory insufficiency have been reported even with therapeutic doses [54, 55]. Dysphagia is more common when cervical muscles are injected. Rates of dysphagia and dry mouth may vary among different preparations/brands [56]. There can be diffusion of toxin to local muscles that are not targeted. As with phenol, it is important to clarify the specific goals of treatment prior to the procedure [53]. In RCTs, botulinum toxin A has been demonstrated to reduce upper limb spasticity in individuals with stroke and brain injury [57, 58] and to improve muscle tone and performance on specific simple functional tasks, such as putting an arm through a sleeve, cleaning the palm of the hand, or cutting the fingernails [54]. Improvement in lower limb spasticity can also be achieved with injections of botulinum

toxin A in individuals with stroke and brain injury [58, 59]. RimabotulinumtoxinB has also been demonstrated to improve upper limb spasticity after TBI or stroke [60]. When used for cervical dystonia, however, there may be a higher incidence of dysphagia and dry mouth with the use of botulinum toxin B compared to botulinum toxin A [61]. The botulinum toxin preparations available in the USA are FDA approved for certain dystonias in adults and detrusor or bladder overactivity. Onabotulinum toxin A is approved for spasticity of the thumb, fingers, wrist, elbow flexors, toes, and ankle plantar flexors in adults; but it is commonly used in other muscles "off-label."

In an open study, selective tibial motor neurotomy was shown to decrease spasticity and improve dorsiflexion strength and gait on a long-term basis (at least 2 years) in patients with hemiplegia. Plantar flexion strength eventually returned to baseline due to collateral sprouting, while decreased spasticity is maintained due to the inability of IA afferents to reconnect at the spinal cord level [62].

Local anesthetic nerve blocks can be used as a "test run" before using botulinum toxin, phenol, or neurotomy in order to ascertain whether or not reducing tone in a muscle or group of muscles will provide any benefit or adversely affect function. Local anesthetic blocks can be helpful when there is a question of whether the inability to move a joint beyond a certain range of motion is due to severe hypertonia or contracture. The local anesthetic trial is, of course, no guarantee, as it is not likely to be exactly comparable to the other procedures [21, 53].

Baclofen pumps can also reduce spastic hypertonia in people with TBI [63, 64] by delivering small quantities of baclofen directly to the intrathecal space, thus avoiding the systemic effects of baclofen. A potentially life-threatening withdrawal syndrome with high fever, altered mental status, and muscular rigidity can occur if the baclofen is suddenly cut off, either because the reservoir is depleted or there is a malfunction in the pump or catheter [65]. Regular visits for refills must be scheduled. Today's pumps have alarms that alert the patient that the pump is in danger of becoming empty.

There are also orthopedic procedures, such as muscle and tendon lengthenings and transfers, which help to decrease muscle tone. Lengthenings are done in the context of treating contractures. A small study in individuals with stroke and TBI demonstrated tendon fractional lengthening of the pectoralis major, latissimus dorsi, and teres major improved both passive and active shoulder flexion, abduction, and external rotation and reduced pain [66]. Tendon transfers are usually done for the purpose of improving function. The split lateral anterior tibialis tendon transfer for the treatment of ankle-foot inversion is an example. The tibialis anterior tendon is split at its insertion, and half of it is taken from the medial side of the foot and implanted on the lateral foot, such that it is now balancing the inversion with an eversion pull, thereby dorsiflexing the ankle in a neutral position [67, 68]. When ankle plantar flexion contracture accompanies inversion, the Achilles tendon is lengthened as well. In order to preserve the ankle plantar flexion strength, the flexor digitorum longus and flexor hallucis longus can be transferred to the calcaneus [67]. Surgeons and referring clinicians must beware of the possibility of overcorrection resulting in the dominance of antagonist muscles, both with lengthening and transfers [68].

Persistent hypertonia and/or immobility can result in contractures. The main approaches to the prevention of contractures are range of motion exercises and proper positioning. Other approaches to spasticity and dystonia referred to above may be necessary as well. If contractures have developed, serial casting is an excellent way of reducing them. A cast is placed with the limb in close to the full achievable range of motion and left on for 3–7 days. Muscle tone will be reduced. When the cast is removed, there will often be more passive range of motion available. Another cast is placed that takes advantage of these additional gains. This process continues until no additional range of motion is achieved [37, 69]. However, the reduction of contractures in response to serial casting in patients with TBI may be transient [70, 71]. Botulinum toxin injections to reduce spasticity prior to casting have been found to help sustain the results in children

with cerebral palsy [72, 73]. Long-term studies of botulinum toxin injections, combined with serial casting, in adults or children with TBI need to be done.

When serial casting is not feasible, adjustable spring-loaded dynamic orthotics can be used to place maximum tolerable tension on the contracted soft tissues, with gradual changes in joint angle and tension being made overtime [74, 75]. These orthotics have the advantage that the skin can more easily be observed for pressure ulcers, but they are not as effective as casting, partly because the patient can remove them. When these approaches fail, surgical lengthenings may be indicated.

Heterotopic ossification (HO) in the large joints is not uncommon among people with severe TBI. It is associated with longer duration of coma, longer period of mechanical ventilation, surgically treated fractures of the extremities, and the development of autonomic dysregulation [76]. HO can be extremely painful during range of motion exercises. Patients may be very resistant to range of motion exercises while HO is forming. HO often progresses to complete ankylosis of joints. It can entrap peripheral nerves with resultant neuropathy. Disodium etidronate and nonsteroidal anti-inflammatory drugs (NSAIDs) have both been used for prevention, although the evidence for their beneficial effect is largely from studies in other patient populations, such as spinal cord injury and hip surgery [77, 78]. There is, in particular, an unanswered question as to whether the preventive effect of etidronate is only short term [79]. Although disodium etidronate is generally well tolerated with serious side effects being rare, NSAIDs can cause gastric and duodenal ulcers and, less commonly, adverse cardiac events [77]. Some physicians use etidronate or NSAIDs prophylactically in people who have been in coma, vegetative state, or minimally conscious state for significant periods of time (the populations at increased risk of developing HO) [80]. Other clinicians will wait until there are symptoms. Usually HO begins with an inflammatory response resulting in a painful, warm, swollen, and erythematous area. It can be mistaken for a deep vein thrombosis (DVT), cellulitis, or deeper infection. Alkaline phosphatase and creatine phosphokinase will generally be elevated. At that point, it will not show up on an X-ray, but a triple-phase bone scan will be positive. It can take 3–4 weeks before it becomes calcified sufficiently to be seen on an X-ray. Some physicians get bone scans when the inflammatory response is seen and DVT is ruled out; and if there is uptake on the bone scan in that area, then they will start disodium etidronate or an NSAID or administer radiation, another treatment that has been effective in patients with SCI or following hip surgery. Once formed, the HO often restricts range of motion or fuses a joint. A retrospective review of surgical excision of shoulder HO in a small cohort of patients with TBI demonstrated significant improvements in all planes of shoulder motion, improved functional status, and increased independence with feeding, grooming, and toiletry [81]. There is no evidence that waiting more than a year after injury to do a surgical excision is associated with a decreased chance of recurrence [82]. Disodium etidronate, NSAIDs, and/or radiation can be effective for the prevention of recurrence after surgery [77, 78, 83]. There are also case studies suggesting the use of extracorporeal shock wave therapy as a therapeutic invention to improve range of motion by way of reducing pain from HO [84, 85], but more robust studies are needed to clearly demonstrate its effectiveness.

Dysphagia

Dysphagia is a common disorder following TBI. Dysphagia is dependent on the status of the oral-motor musculature as evaluated by modified barium swallow (MBS) [86, 87], but also on the patient's cognitive status [88]. Lack of basic orientation and the inability to follow commands are predictive of aspiration [89]. Even among patients with higher levels of cognitive function, poor self-monitoring and impulse control can affect swallowing ability due to difficulty monitoring bolus size and speed of swallowing. Other predictors of dysphagia following TBI include RLAS score, GCS score on admission, presence

of a tracheostomy, and longer ventilation time [86, 88, 90]. It is not necessary to be feeding orally to develop pneumonia in the early stages of recovery; and, in fact, one study found that 81% of people with TBI who developed pneumonia were not receiving anything by mouth [90]. One can aspirate secretions and refluxed or regurgitated stomach contents; and respiratory insufficiency, inadequate or absent cough, and lack of mobility can cause or contribute to pneumonia as well. One study found that 41% of patients with TBI who aspirated were found to do so silently, i.e., without coughing [86]. Disability rating scale score, RLAS score, and oral-motor disorders on MBS are predictors of aspiration at 1 year after TBI [86, 87]. The MBS is considered the standard for evaluating swallowing. Even individuals with tracheostomy can undergo MBS and start treatment for swallowing [91]. Fiber-optic endoscopic evaluation of swallowing (FEES) can also be used for a better view of the pharynx [92].

The management of dysphagia involves trials of food and liquid consistencies as determined by MBS. Head and neck postural techniques and exercises, both tailored to the individual aspect of swallowing that is disordered, can improve performance [92]. In an RCT, 55% of patients with TBI and stroke with neurogenic dysphagia avoided aspiration with a chin-down posture as demonstrated by video fluoroscopy. However, of the 51% of study participants who were silent aspirators, 48% continued to demonstrate aspiration despite the chin-down posture [93]. The use of neuromuscular electrical stimulation in combination with conventional swallowing therapy may be an effective intervention to accelerate improvement in swallowing function as demonstrated in a small RCT of 20 participants (14 stroke and 6 severe TBI) with neurological oropharyngeal dysphagia [94].

Cognitive Disorders

Cognitive Rehabilitation

Cognitive impairment will usually improve during the first or second year following TBI and sometimes up to 5 or 10 years post-injury [95]. Disturbances in the sleep-wake cycle are common after TBI, and sleep architecture and quantity and quality of sleep are associated with functional recovery [96]. Poor nocturnal sleep and daytime sleepiness in individuals with TBI have been correlated with impaired performance in cognitive domains such as attention, memory, and processing speed [96–100]. There are also interactions between sleep-wake disturbances and post-TBI pain, depression, and anxiety [101–103]. Pharmacologic interventions for sleep-wake disturbance for individuals who have sustained a TBI are currently under active investigation, and so far results have been varied (see Chap. 7). There is preliminary evidence to suggest that individualized treatment of sleep-wake disturbance using a combination of sleep hygiene strategies and pharmacologic interventions may reduce the severity of insomnia and improve language and processing, but such studies have been small and uncontrolled [104].

There are several aspects of cognition for which there is evidence for the benefit of therapeutic interventions. Processing speed, reaction time, attention, and response inhibition are commonly impaired following TBI [105]. A meta-analysis of 12 RCTs (237 individuals with stroke, 146 individuals with TBI, and 201 individuals with malignancy impacting the CNS) on the use of cognitive interventions for attention rehabilitation found short-term improvements in divided attention among individuals with stroke, but no significant improvements in sustained or selective attention or inhibition in individuals with TBI [106]. The duration of cognitive interventions ranged from 20 min to 7.5 h per week. However, of the four studies that reported long-term outcomes (follow-up of 2–12 months), there were no sustained effects from the interventions on selective attention, sustained attention, alternating attention, or inhibition in either the stroke or TBI populations [107–110].

Overall, memory impairment following TBI will demonstrate some degree of spontaneous improvement overtime, and cognitive rehabilitation strategies for memory can serve as effective treatment adjuncts [111]. The international

cognitive (INCOG) expert panel guidelines recommend the use of both internal and external compensatory strategies to improve memory [112]. For the treatment of memory disorders, there is some evidence for the benefit of teaching semantic strategies to people with TBI [113, 114]. This includes semantic association, semantic clustering, and semantic elaboration. Training in visualization and visual imagery techniques can be beneficial for people with mild memory problems [115, 116]. Preliminary evidence suggests that following severe TBI, retrieval practice, whereby individuals are quizzed on newly learned information, improves delayed recall after both short (30 min) and long delays (1 week) [117]. Working memory capacity is associated with effective learning ability after TBI, and further study is warranted [118]. External aids such as notebooks and appointment books can be quite helpful and are recommended [119–122]. For those who can learn their use, even in a limited fashion, tablet computers or "smart" mobile phones are often more useful than notebooks [123–127]. These can be programmed with reminder alarms and, therefore, do not rely on prospective memory as do appointment books. They may have to be programmed by somebody else if the person with TBI does not have the requisite skills, and some people with TBI need others to remind them to use the device [123]. Pagers are another external compensatory aid that have been found to be successful [128, 129]. There is evidence that therapy focused on metacognitive strategies and problem-solving skills may be effective in improving post-TBI executive function [130–133].

The effectiveness of therapies to improve hemi-inattention and aphasia has been largely demonstrated in subjects with stroke. It is not unreasonable to tentatively extrapolate to people with TBI until the evidence is available with this population. Spatial neglect, often, but not always, of the left side, can be decreased with consistent cueing to scan to the neglected side [120, 134]. Aphasia has been treated with functional language stimulation, cueing, and semantic analysis in people with stroke. The evidence suggests that such training is effective, but studies are not yet definitive [121, 135, 136]. There is limited evidence for the effectiveness of constraint-induced language therapy (CILT) in the chronic phase after stroke [135, 137–139]. In CILT, the person being trained is not allowed to use gestures or to write and is forced to communicate during a simple card game, for instance. A screen can be put up so that gestures cannot be seen. The person being trained has to initially have some language function, such as the ability to say the number on a card. One study demonstrated a positive effect of CILT and the NMDA receptor antagonist memantine used separately for the treatment of aphasia and a greater effect when used in combination [139]. There is limited evidence for the benefit of dextroamphetamine for the treatment of aphasia in the context of speech therapy [140].

There is also evidence for the efficacy of holistic cognitive rehabilitation programs in which cognitive, emotional, motivational, and social functions are addressed in a single program. Gains have been seen in employment and in community integration skills [141]. The use of telehealth services to administer cognitive therapy interventions has been demonstrated to increase treatment adherence in individuals with mild traumatic brain injury (mTBI) [142] and may be a promising means of reducing treatment barriers in the TBI population.

When a patient has problems with alertness, initiation, and/or attention, medical factors may need to be treated. Infection, electrolyte imbalance, and hydrocephalus can result in decreased arousal, attention, and initiation. Endocrine dysfunction is common and is addressed in Chap. 11. In one study of patients with disorders of consciousness secondary to TBI, more than 80% of 184 patients experienced at least one medical complication during inpatient rehabilitation [143]. Insomnia and other sleep disorders are also frequently seen after TBI [144] and are further addressed in Chap. 7. A prospective longitudinal study found that 67% of patients with TBI have persistent sleep-wake disturbances even 3 years post-injury [145]. Poor sleep, vitamin D deficiency, and anxiety are also commonly associated with chronic fatigue after TBI [146]. Conversely, fatigue also predicts anxiety, depression, and daytime sleepiness [147] and contributes to self-reported disability after TBI

[148]. There is evidence that treatment with high-intensity blue light therapy may help to alleviate fatigue and daytime sleepiness in patients with TBI [149]. Seizures can result in postictal lethargy and is also addressed in Chap. 10.

Pharmacological Treatment of Cognitive Disorders

Pharmacological approaches can be useful, particularly for treating arousal, attention, initiation, and other aspects of executive skills. The first pharmacologic intervention to consider is withdrawing offending agents, such as phenobarbital [45, 46, 150], phenytoin [46, 150, 151], carbamazepine [46, 151, 152], topiramate [45, 46, 153–159], zonisamide [46], pregabalin [46, 160], baclofen [42, 43], tizanidine [35], benzodiazepines [161], tricyclic antidepressants [162], opiates [163], and antipsychotics (especially the typical antipsychotics, such as haloperidol, chlorpromazine, and thiothixene) [162]. Among the anticonvulsants, levetiracetam [152, 159], gabapentin [46], tiagabine [46], vigabatrin [46], and lamotrigine [46] are relatively free of adverse cognitive effects, although sedation can be an issue with levetiracetam [150] and gabapentin. Studies on valproic acid [46, 164] and oxcarbazepine [46] are mixed with respect to their effect on cognition.

The benefit that a medication is providing must be weighed against the probability that it is causing cognitive impairment. Individual responses to medications vary considerably, so any change seen or not seen when the patient started the medication is important in determining whether it is causing adverse effects.

Insomnia is often a contributor to daytime sleepiness and cognitive impairment. When simple sleep hygiene approaches are not working, medications may be helpful. However, for the long term, if the patient is capable of participating effectively, cognitive behavioral therapy (CBT) is usually more beneficial than medications [165]. See Chap. 7 for further discussion of sleep disorders.

When other causes of attention, arousal, or initiation problems have been addressed to whatever extent possible, stimulants or stimulant-like drugs can be useful. The use of all medications discussed here is "off-label." This includes methylphenidate, amphetamines, modafinil, atomoxetine, dopaminergic drugs, NMDA receptor antagonists such as amantadine and memantine, and cholinesterase inhibitors. Methylphenidate has the best evidence for effectiveness in treating attention following TBI. RCTs have shown gains in on-task behavior and speed of processing, as well as improvement in fatigue, with administration of methylphenidate [166–170]. Methylphenidate comes in both immediate-release and long-acting formulations (see Table 1) [171]. Amphetamines have a similar mechanism of action, but have not been as well studied for the treatment of attention, initiation, or arousal deficits in people with brain injury. Lisdexamfetamine dimesylate, a prodrug

Table 1 Some long-acting formulations of methylphenidate

Drug taken once daily	Mechanism	Peaks (hours)[a]	Duration of action (hours)[a]
Metadate CD ER Capsules (UCB)	Beaded IR and ER MP, double-pulse release	1.5, 4.5	8–12
Ritalin LA (Novartis)	Beaded MP, double-pulse release, IR/DR	1–3, 5–7	
Concerta ER Tablets (Janssen)	Drug overcoat dissolves; then two internal layers gradually release drug	1–2, 6–8	10–12
Daytrana transdermal patch (Shire)	Multipolymeric adhesive – transdermal absorption	8, 10[b]	11.5[b]
Focalin XR (Novartis) (dexmethylphenidate)	Beaded MP, double-pulse release, second release at 4 h, IR/DR	1.5, 6.5	8–12

Data from: Refs. [340–346]

MP methylphenidate, *IR* immediate release, *ER* extended release, *DR* delayed release

[a]Most studies have been done in children

[b]Assuming 9-hour wearing time, peaks at 10 hours on first application, 8 h after multiple applications; includes 2-hour delay until MP appears in plasma

of dextroamphetamine, has been shown in a small RCT to improve measures of sustained attention, working memory, response speed, and some areas of executive function in participants with moderate to severe TBI at least 6 months prior. It also resulted in gains in more persistent difficulties with focused or sustained attention [172].

Amantadine can be effective for hastening, and perhaps improving, the responsiveness of individuals in a minimally conscious state during the first few months after injury [173, 174]. There is more limited evidence for an effect of amantadine on the outcome of inpatient rehabilitation [169, 175]. Although modafinil did not bring about improvement in fatigue and alertness following TBI in one small RCT [176], in another RCT, sleepiness but not fatigue improved [177]. Atomoxetine, a selective norepinephrine reuptake inhibitor, did not result in significant improvement on measures of attention in participants with moderate to severe TBI [178].

There is some evidence that acetylcholinesterase inhibitors can have a positive effect on sustained attention and anterograde memory in people with TBI [140, 169, 179, 180]. A study of rivastigmine in persons with TBI showed no benefit for the group as a whole, but positive results for visual processing speed latency and memory among those with moderate to severe injury in a secondary analysis [181]. Bromocriptine was shown to help dual-task attention in an early study [182], but this result was not replicated by Whyte and coauthors [183]. In the latter study, other aspects of attention also did not improve with bromocriptine. Protriptyline is a stimulating antidepressant that can be activating [184] but has not been well studied.

Behavioral and Emotional Disorders

Treating behavioral and emotional disorders requires an evaluation of the underlying contributing factors. Medical conditions such as electrolyte disturbance, endocrine disorders, infection, hydrocephalus, epilepsy, and others can cause behavioral changes. The loss of control that comes with being physically or cognitively disabled often results in depression and anxiety. Preinjury psychiatric issues often continue to play a role after a TBI. Staff, family, or friends may inadvertently reinforce aggressive and disruptive behaviors by paying undue attention to them. Antecedents to aggression must be evaluated to determine the triggers to such behavior.

Differential Diagnosis of Behavioral and Emotional Disorders

There are a number of behavioral disorders that are often seen after TBI. Sabaz and colleagues [185] reported an overall 54% prevalence rate of challenging behaviors. Disinhibition, aggression, and emotional dyscontrol are extremely common [186], usually as a result of frontal lobe lesions. Apathy is common [187], as are depression [188, 189] and anxiety [189, 190], often as a reaction to the disability once the person develops enough awareness. Posttraumatic stress disorder (PTSD) following TBI can also be seen, even among those with moderate to severe injury, especially in military populations. See Chaps. 13 and 15. Up to 66% of cases occur with delayed onset, peaking between 6 and 12 months post-injury [191]. PTSD is associated with shorter duration of posttraumatic amnesia (PTA), other concurrent psychiatric disorders, and lower functional and quality of life outcome scores following TBI [192]. Psychotic behaviors resulting from TBI are unusual, but do occur. New onset of mania is seen rarely.

Clinicians must be careful not to mistake the influences of cognitive and perceptual deficits for psychiatric syndromes. For instance, reduplicative phenomena caused by frontal dysfunction often include the belief that certain people are imposters. However, this can easily be mistaken for delusional thinking as seen in more classical psychiatric settings. Memory disorders can cause what appear to be hallucinations or delusions. A person with a severe memory disorder may, for instance, believe that someone important to them who has died is actually alive because he or she has no memory of the person's death, particularly if it occurred shortly before

the injury. Visual-perceptual impairment, especially in the context of executive dysfunction, can result in hallucinatory-like experiences. There can be a fine line between these sorts of behaviors and manifestations of actual psychosis. This is an important consideration because it may involve a decision about whether or not to use antipsychotic medication. There are no studies that address this issue, so the clinician has to use his or her best judgment. One consideration is whether or not there is significant emotion, in particular, fear, surrounding a belief. For example, if the person with TBI fears that they will be hurt by someone or something that they see or believe to exist, one would be more apt to treat it as a psychotic behavior than if the person is unconcerned. Other combinations of cognitive, behavioral, and perceptual problems can mimic psychiatric syndromes. Neurologically based apathy can mimic depression, except that the withdrawn, apathetic patient will not feel sad or be tearful [193].

Nursing and therapy staff or other caregivers will often be in the best position to provide information to physicians, psychologists, and social workers that may provide clues to the etiology of behaviors. They will often be the ones to hear the despairing words of a depressed patient, to observe that a patient does not initiate and shows little affect, to see the circumstances under which a person becomes aggressive, or to see whether fearfulness is associated with hallucinatory or delusional-like behaviors. They can see the degree to which a behavior is interfering with rehabilitation or causing disruption to the patient or to others' lives. Of course, this does not mean that the clinician should rely entirely upon others to evaluate behavior. Interviewing even very impaired patients can turn up clues that aid in diagnosis, and observing them in therapies or on the nursing unit can also be revealing.

Treatment of Mood and Anxiety Disorders

Some people with depression and/or anxiety following TBI can benefit from individual counseling despite some cognitive impairment [194]. Cognitive behavior therapy has been found to be helpful in treating distress following acquired brain injury [195]. However, problems with executive function, attention, and memory can be limiting factors. CBT directed at improving depression or anxiety has demonstrated some success in the TBI population [196, 197] and may be more effective in combination with motivational interviewing [198]. However, in one study, CBT had no significant effect on suicidal ideation [199]. An RCT also demonstrated no differences in efficacy between CBT and supportive psychotherapy for depression following TBI [188]. Group treatments can sometimes be helpful as well. A periodic telephone call inquiring about problems, providing needed information, and facilitating problem-solving has been found to be preventive of future depression and also to treat preexisting depression [200].

Medications can be used when depressive symptoms and/or anxiety interferes with quality of life and/or rehabilitation over a sustained period of time. Depression is best treated with low- or non-sedating antidepressants – the selective serotonin reuptake inhibitors (SSRIs) and SNRIs [169]. In a systematic review and meta-analysis, pharmacologic treatment of depression after TBI was found to be associated with significant reductions in depressive symptoms [201]. However, there was no difference in preventing a relapse of depression following TBI by continuing therapy with citalopram, a selective serotonin reuptake inhibitor, compared with placebo [202]. Antidepressants should be used cautiously, especially in the elderly, as SSRIs (and tricyclic antidepressants) have been associated with increased mortality and hemorrhagic stroke [203, 204]. This fact, however, must be weighed against quality of life issues and the known risk of cardiovascular disease and suicide in untreated depression [204]. Anxiety can also be treated with these medications. Benzodiazepines are best avoided when possible due to their adverse effect on alertness, attention, and memory, though occasionally the trade-off can be in favor of their use since anxiety itself can affect cognition. Buspirone is unlikely to cause cognitive side effects [205].

Treatment of Behavioral Disorders

Treating behavioral issues following TBI requires understanding and addressing both antecedents to and consequences of the individual's behavior [206]. Treating other aspects of disability, facilitating communication, and providing opportunities for enjoyable and productive activities can resolve some of the causes of disruptive behaviors, improve mood, and allow the person with TBI to feel more in control, with resultant decreases in aggressive and disruptive behavior. Along these lines, a review of approaches to social and behavioral dysfunction after acquired brain injury concluded that comprehensive holistic rehabilitation programs are more effective than both cognitive behavioral therapy (CBT) and applied behavioral analysis [207]. A patient's environment should be considered as well, including reduction of physical barriers to function and addressing the influences of those around him or her who may be provoking antisocial behavior. Behavioral interventions to address aggressive behavior should provide natural consequences (e.g., cleaning up and paying for broken items) whenever possible and should avoid reinforcing disruptive behavior. The individual must be taught alternative approaches to expressing him-/herself and getting his/her needs met [206]. Positive consequences for pro-social behavior can be put in place by exploring what would be rewarding to the person in question. Some programs use point systems or tokens that can be exchanged for rewards. There is a natural tendency for healthcare professionals and family members to pay attention to patients who are, for instance, shouting and shaking the bed rails or demanding something that cannot be provided. If, after addressing antecedents and consequences, a disruptive behavior continues, caregivers may have to give the patient "time-outs" from reinforcement of those disruptive behaviors [208]. To treat the executive dysfunction that is behind aggressive behavior, therapists must increase the awareness of the patient's own internal reactions by teaching self-monitoring techniques, providing feedback, and having them do self-evaluations. This type of training has been shown to result in decreased expression of anger and improved socialization in one study [209]. Paradoxically, the person's awareness of his or her reactions did not have to increase for the therapy to be effective. This finding requires verification. There is also limited evidence for the use of anger self-management training or psychoeducational treatment for anger and irritability [210].

At times, pharmacologic intervention is helpful. Treating underlying problems with arousal, initiation, and attentional disorders can have a secondary effect on irritability and disruptive behavior. Studies of methylphenidate to treat aggression ("off-label") have been of limited quality and mixed in their outcomes [211]. Treating depression and anxiety can also have an ameliorating effect on irritability and aggressive and disruptive behavior. The effect of antidepressants on aggressive behavior (not necessarily in the context of depression, therefore "off-label") has been studied, but the evidence for their efficacy is limited [211]. The pharmacologic treatment of aggression caused by disinhibition has been poorly studied [169], and all pharmacological uses are "off-label." Therefore, among the medications that may be useful for this condition, it is best to start with medications that have the fewest cognitive side effects. In a single-site, randomized, double-blind, placebo-controlled trial, amantadine has been demonstrated to reduce irritability and aggression at 28 days compared to placebo in a cohort of patients who were more than 6 months post-TBI [212]. In a large multicenter trial, participants in both the amantadine and placebo groups demonstrated improvements in observer-rated irritability at both 28 and 60 days; however, there were no between-group differences at either time interval [213].

Some anticonvulsants (valproic acid, carbamazepine, gabapentin, and lamotrigine) have been used for treating aggression and agitation [214]. However, there are no well-controlled studies demonstrating the efficacy of anticonvulsants [211, 215]. Levetiracetam can cause impulsive, irritable, and aggressive behavior [45]. There are studies suggesting that beta-blockers can be helpful [152]. It can take considerable time to reach therapeutic doses while the patient accommodates

to the changes in blood pressure and heart rate [211, 215]. Pindolol is a beta-blocker with partial adrenergic agonist effect (intrinsic sympathomimetic activity) such that it prevents blood pressure and heart rate from dropping below normal. In a small double-blind, placebo-controlled crossover study of people with ABI and severe aggressive behavior, it was found to significantly reduce aggressive behavior without causing sedation [216]. Beta-blockers have been found to cause cognitive decline in the elderly [217], and they can also cause fatigue and sedation [218]. Buspirone [211, 215] and lithium [169, 171, 219] have been used as well, although controlled studies in people with brain injury are lacking [211, 215]. The antipsychotics [169] can be used for more severe aggressive behaviors when other medications have not been effective or when relatively rapid control of behavior is needed because of the danger that someone will be harmed. There is some limited evidence for their efficacy in treating aggressive behavior [220]. However, they can cause Parkinsonian symptoms, dystonias, and tardive dyskinesia [211]. The atypical antipsychotics, which may have fewer motor side effects, can result in weight gain, dyslipidemia, and insulin resistance [221]. Both typical and atypical antipsychotics have been found to be associated with sudden death in elderly populations [222–224]. If they are to be used for an extended period of time, it is best to get a fasting blood sugar, lipid profile, and EKG before or shortly after starting them. Benzodiazepines are sometimes also used for situations in which relatively rapid control of aggressive behavior is needed. However, some authors believe that benzodiazepines can themselves cause disinhibition and agitated behavior [225]. As noted above, they can result in memory and attentional dysfunction and increase confusion. Even when they are helpful in the short term, this is often due to their sedating effect [211]. Their use can result in a pattern in which the patient is either sleepy or agitated. This results in other medications needing to be used to replace the benzodiazepine, and/or behavior plans must be put in place to reduce the aggressive behavior.

Social Support and Motivation

Social support is also an important element to success in rehabilitation, as it provides incentive and motivation to continue with what is usually a difficult ordeal. Motivation, but not physical capacity, is a strong predictor of physical activity levels in patients with TBI 6 weeks following discharge from inpatient rehabilitation [226]. Motivation and engagement are key to the success of rehabilitation, yet can be elusive, particularly following TBI when initiation, insight, or self-awareness is impaired [227]. Motivational interviewing, which is a nonconfrontational approach that allows the patient to take the lead and, thereby, fosters self-efficacy, can be effective with some individuals [228]. Bell and colleagues [229] found that a periodic telephone call that included motivational interviewing, counseling, education, and follow-up of various aspects of care resulted in improved functional outcomes and quality of life, although the results were not replicated in a multicenter randomized controlled trial [230].

Community Reintegration

Social, vocational, and community reintegration goals are important for individuals following TBI. Social communication abilities and behavioral functioning are factors that impact successful social integration post-TBI [231]. Return to work can be particularly challenging for individuals after TBI, and approximately 60% of working-age individuals (ages 16–60) remain unemployed at 2 years post-injury [232, 233]. Similarly, in an Australian study, only 44% of individuals remained employed within 3 years after moderate to severe TBI [234]. A systematic review identified access to transportation, access to services, participation in social interaction, the number of post-concussion symptoms (PCSs), fatigue, self-reported physical competence, subjective well-being, and pain to be possible predictors of employment outcomes [235]. Increased severity of TBI, older age, pre-injury psychological treatment, pre-injury student or

"blue-collar" employment, and pre-injury substance use are also associated with poor employment outcomes [232, 233, 236]. There may be a decline in the probability of post-TBI employment between 5 and 10 years post-injury [223, 233]. However, an Australian study showed an increase in employment between 2 and 5 years post-injury followed by a plateau from year 5 to year 10 [236]. Return to driving after TBI is also challenging, but can confer a large degree of independence if successful return to driving is achieved. Individuals with TBI who are driving a vehicle at 1-year follow-up are more likely to be employed at 2-year follow-up [237]. However, specific rehabilitation for return to driving with driving evaluations and road safety tests is often needed as the risk of involvement in traffic accidents with personal responsibility also increases after return to driving post-severe TBI [238].

The extent to which an employer is supportive following a TBI can be crucial to successful return to work for all severities. Vocational counselors can facilitate communication between the patient and the workplace. Therapies should attempt to simulate workplace tasks, although if the employer is cooperative, it may be better to return the person to work and have them coached and trained on the job. A gradual return to work can ease the transition [239]. Assistance with coordinating the return to work will often be needed, including on-the-job training and contact with the employer [240, 241]. The quality of studies on vocational interventions is low [242].

Caregiver Stress

Families of people with TBI are often under considerable emotional stress, especially when in caregiver roles [243–245]. Feelings of loneliness and caring for someone with severe disability are associated with higher caregiver burden [246]. Additionally, the presence of more functional impairment, neurobehavioral problems, and drug use in the TBI patient is associated with reduced caregiver life satisfaction in the first 2 years following injury [247]. The well-being of caregivers also has a reciprocal impact on the psychological well-being of those with TBI [248]. It is therefore important to educate caregivers about TBI and to provide them with lists of resources (e.g., brain injury associations, governmental programs, healthcare providers) that they may find useful so that they are equipped to cope with whatever issues arise. A randomized controlled trial of a telephone-based intervention comprised of individualized education and mentored problem-solving sessions focusing on the primary concerns of caregivers demonstrated improved caregiver outcomes with more active coping and less emotional venting [249]. Caregivers should also be encouraged to seek support via support groups, counseling, religious institutions, and friends [250, 251].

Mild Traumatic Brain Injury

Definition and Diagnosis

The definition of mild traumatic brain injury (mTBI) found in the literature has varied somewhat, but a widely used definition is that formulated by the Mild TBI Task Force of the American Congress of Rehabilitation Medicine [252]:

> a traumatically induced physiological disruption of brain function, as manifested by *at least* one of the following:
>
> 1) any period of loss of consciousness;
> 2) any loss of memory for events immediately before or after the accident;
> 3) any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and
> 4) focal neurologic deficit(s) which may or may not be transient;
>
> but where the severity of injury does not exceed the following: loss of consciousness of approximately thirty minutes or less; after thirty minutes, an initial Glasgow Coma Scale of 13-15; and posttraumatic amnesia not greater than 24 hours (Mild Traumatic Brain Injury Committee of the Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine 1993).

Making the diagnosis of mTBI can be a difficult undertaking with a number of potential pitfalls. The patient's memory of or inferences about what occurred may be inaccurate. Medical records may not reflect a period of LOC or post-traumatic amnesia (PTA) that occurred before medical personnel arrived at the scene. The GCS may not have been assessed or reassessed until more than 30 min has passed. There is a potential problem with the overlap of the acute signs and symptoms of mTBI with acute stress reactions that commonly cause people to be "dazed, disoriented, or confused" after a major physical and/or psychological trauma that may include a brush with death. The clinician must obtain the most objective information available (e.g., emergency medical records, accounts of observers), ask probing questions, and listen carefully to the patient's account and then use his or her judgment to sort out the etiology(ies) [253]. There are times when it is impossible to make the distinction between acute stress and mild TBI or both may have existed simultaneously. Neuroimaging such as diffusion tensor imaging (DTI), SPECT, and PET [254, 255] and serum or cerebrospinal fluid biomarkers such as S100B, neurofilament light, and tau protein are promising approaches to confirming that a patient has had a brain injury and/or that there is longstanding structural change [256]. However, there is disagreement among some studies; and additional work is needed to determine the ideal biomarker or combination of biomarkers with good sensitivity and specificity for brain injury, long-term cognitive impairment, and other persistent PCSs [255–257].

Post-concussion Symptoms

mTBI can be associated with a variety of symptoms; and the term "post-concussion syndrome" has frequently been used to describe the complex of cognitive, physical, and emotional complaints that can occur. Some have argued that these symptoms do not manifest in a specific set, but rather can occur in various combinations of one or two symptoms to many symptoms and should, therefore, not be referred to as a "syndrome" [258]. They are probably best referred to as "post-concussion symptoms" (PCSs) or "post-concussion disorders." That being said, most studies of PCSs use the "syndrome" as defined by one of the versions of the International Classification of Diseases (ICD) or Diagnostic and Statistical Manual of Mental Disorders, the Rivermead Post-concussion Symptom Questionnaire, or other survey instruments [259]. The most frequent complaints are fatigue, forgetfulness, difficulty concentrating, headaches, dizziness, irritability, insomnia, depression, and anxiety. They have been said to persist in 9–15% of people with mTBI [260, 261], but higher and lower estimates exist as well [262, 263]. These statistics depend very much on the number of symptoms that are required for inclusion, the timeframe for the use of the word "persistent," and the population studied [262]. Symptom frequency diminishes overtime, and it is controversial whether the symptoms can continue indefinitely or are the result of litigation or psychological factors when persistent. They can, of course, be seen in people with moderate or severe TBI and are in fact common complaints of people who have never had a TBI [264, 265]. A study of people with mTBI occurring 22–35 months earlier and sex- and age-matched controls who had presented to the emergency room with minor non-head injuries (also matched by time from injury) was done in Lithuania, where compensation is not much of an issue. It was found that there was no significant difference between the frequency of complaints that could be attributed to a TBI in the group that had mTBI compared with the control group, except for depression, alcohol intolerance, and worry about having a brain injury. However, there were trends toward more complaints of "sporadic memory problems" in the mTBI group ($p = 0.052$) and toward more frequent endorsement of "no concentration problems" in the control group ($p = 0.079$) [266]. In fact, most studies using controls with orthopedic injuries find that having had a mTBI does not predict persistent PCSs (usually said to be those symptoms that continue for at least 3 months), while pre-injury psychiatric history, early post-injury anxiety, and pre-injury physical health are

the best predictors of persistent symptoms [267–270]. Another study found older age, preexisting psychiatric conditions, lower education, injury caused by assault, extracranial injuries, and lower GCS were predictive of worse functional outcome [271]. Other studies have found persistent PCSs or persistent post-concussion syndrome to be associated with both pre- and post-injury psychological issues [264, 272–276]. Hou and colleagues studied patients who had a mTBI without a control group and found that risk of persistent post-concussion syndrome (by ICD-10 criteria) was associated with negative mTBI perceptions, stress, anxiety, depression, and all-or-nothing behavior. In a study by Wilk and colleagues [277], blast injuries in a military context that resulted in mTBI without loss of consciousness were not associated with PCSs 3–6 months after the injury, whereas TBIs with LOC were associated with headaches and tinnitus, but not other PCSs. In a population of active-duty marines, ever having had a concussion was associated with greater emotional distress, but not with persistent PCSs or cognitive impairment. However, having had multiple concussions was associated with greater emotional distress, persistent PCSs, and cognitive dysfunction [278]. Depression is a frequently associated condition. PCSs overlap with the symptoms of posttraumatic stress disorder (PTSD) [260, 262, 264, 272, 275]. This is a major issue in the treatment of military populations, many of whom have blast injuries. As noted above, this is complicated by the fact that acute stress reactions are probably the norm at the time of a blast injury, when the service member may have had a brush with death, may have had severe bodily injury such as loss of a limb, and may have seen other service members killed and/or injured around him or her. Military combatants are likely to feel "dazed" and perhaps confused from emotional trauma at such times. When screened at a later date [279], they may endorse these symptoms and be screened positive on that basis (without clinician confirmation) for mTBI, setting in motion a process that may result in an incorrect diagnosis and treatment if they are actually experiencing PTSD or depression or a combination of mTBI with one or more mental health disorders [260, 272, 275, 280]. The case can be made that some such people would never have sought help for their emotional struggles due to an inability to face their emotional problems and/or the stigma attached to mental health disorders. PTSD is to some extent preventable in people with mTBI with the use of cognitive behavioral therapy during the period of acute stress reaction [281]. mTBI and PTSD in the military are discussed in greater depth in Chaps. 13 and 15.

Studies have shown that healthy control subjects or controls with minor non-head injuries report the frequency of PCSs at a rate higher than what is retrospectively reported by people with mTBI to have been present before their injuries. This has been interpreted to indicate that people with mTBI tend to attribute to the injury symptoms that were in fact present beforehand [266, 282, 283].

It is important to recognize that many of the physical and emotional symptoms associated with mTBI can, themselves, result in cognitive impairment even outside the context of mTBI. Some of the cognitive complaints following concussion may therefore have their origin at least in part from pain, insomnia, depression, and anxiety [284].

Symptoms, such as headaches and dizziness, should be treated symptomatically (see in the following), particularly in the early weeks and months following an mTBI. However, if such symptoms, in particular the cognitive, persist beyond a few months in the absence of other contributing factors (e.g., older age, previous concussions, history of attention-deficit disorder or learning disability – see in the following), the treating clinician should consider a psychological contribution and/or exaggeration related to litigation. However, as is the case with conversion disorder, such diagnoses are often met with considerable resistance and may result in the patient looking elsewhere for care until finding someone who believes them. In the case of psychological etiology, it can be helpful to have a program addressing persistent PCSs that routinely includes a psychological treatment component [262] so that the patient with persistent PCSs can enter this program.

Similar to the questions surrounding the etiology of other post-concussion symptoms, rehabilitation following mTBI is associated with considerable controversy about the expectation for cognitive recovery. The controversy stems from the fact that most prospective, controlled studies of unselected populations that use neuropsychological testing as an outcome measure have indicated that recovery is completed by 3 months after a first uncomplicated concussion [261, 285–287]. Samples taken from outpatient clinics or those including participants in litigation are associated with cognitive impairment beyond 3 months [287], and clinicians frequently see patients with residual cognitive complaints that continue indefinitely, even among non-litigators. There is also a study that found slower processing speed in patients older than 18 compared with comparable controls with orthopedic injuries even 3 months after injury [288].

There is an argument to be made that indeed some people may have longstanding residual cognitive impairment as a result of mTBI apart from any other influences. If such mild impairment existed in one or several hundred people who had concussions, it might take thousands of subjects before a statistically significant effect could be seen in a controlled study or meta-analysis. The number of people who have concussions has been estimated by the CDC to be approximately 1,275,000 annually in the USA (75% of the 1.7 million TBIs) [289, 290], so that the few clinicians who treat large numbers of people with mTBI still might see such patients with persistent PCSs more than occasionally.

There are a few lines of evidence suggesting that concussion can cause such residual cognitive impairment: (1) Studies suggest that multiple concussions might cause permanent findings on neuropsychological testing [278, 291–294]. In order for this to be the case, there has to be a certain amount of neuronal loss in a single concussion that is additive with each new concussion. Of course, the neuronal loss from a single concussion may or may not be enough to cause cognitive impairment. (2) Similarly, people with preexisting learning disabilities are more likely to have lasting cognitive effects from multiple concussions [290]. (3) Concussion has been found to result in worse functional outcomes [295, 296] and to be more likely to cause permanent cognitive deficits in older adults [297], though there is a study suggesting the contrary [298]. This subject is in need of further investigation. (4) Some studies of DTI done in people with mTBI have demonstrated diminished axonal integrity months or years after the injury in some patients [23, 254, 299, 300]. Again, some degree of axonal loss can undoubtedly be incurred without an effect on cognition. Kraus and colleagues [23] found that there was an overlap between the degree of white matter disruption found in people with mTBI and that of people with moderate TBI. On the other hand, Ilvesmaki and coauthors [301] found that abnormal DTI findings were not associated with acute mTBI when patients were compared with age- and gender-matched controls. There were substantial abnormalities among the older control subgroups. (5) There have been studies that have looked at more subtle aspects of cognition after mTBI than are generally evaluated in the studies that showed no change. Dual-task paradigms in particular demonstrate differences in those with histories of concussion compared with controls without concussion. Pare and coauthors [302] and Tapper and coauthors [303] found that reaction time in a dual-task paradigm was still prolonged at 3 months post-injury compared with healthy controls. Another study found subtle learning differences in a sample of non-litigating, working people following mTBI compared with controls [304]. (6) There is evidence that there may be real differences in cognitive complaints of people who have had mTBI in the distant past compared with controls. One study of consecutive patients with mTBI 6 months after injury found fatigue, which could reflect additional attentional resources being mobilized to accomplish the same tasks, to be a more common complaint (32%) among those with mTBI than among controls with minor injuries [305]. The Lithuanian study cited above found trends toward complaints of memory and attention problems in people long after mTBI compared to controls [266]. With a greater number of subjects, these trends may have been significant.

It is possible that a very mild decline in cognitive capacity that would not be clinically significant for most people can play a larger role in the context of diminished cognitive reserve. The cognitive reserve hypothesis suggests that individuals with traits that are associated with lower cognitive function would have a worse cognitive outcome than others with the same injury [260, 306, 307]. As discussed above, among those with mTBI, previous concussions, preexisting learning disability, and older age may be risk factors for persistent neuropsychological decline. As also discussed above, other factors that affect cognition, such as sleep disorders (e.g., insomnia, sleep apnea), persistent pain, or psychological factors (e.g., depression, PTSD), can diminish cognitive reserve such that a mTBI would result in persistent neuropsychological deficits that may not otherwise have been manifested [306]. There is probably a spectrum of patients with respect to persistent cognitive complaints:

1. On one end of the spectrum would be those who had more axonal injury than is typical for a mTBI and whose cognitive deficits result largely from brain injury. Those with GCS scores of 13 may be in this category, though it is possible to have a higher score and still have a more severe injury than is usual.
2. Those patients who have diminished cognitive reserve for any of the variety of reasons discussed above, but who also have significant enough axonal injury to interact with this diminished reserve to result in increased cognitive impairment.
3. Those patients who are otherwise like those in 2 above, but whose recovery is such that they no longer would have significant cognitive disorder were it not for the issues causing diminished cognitive reserve.
4. On the other end of the spectrum are those who had no or insignificant axonal injury and whose cognitive problems result entirely from other causes such as insomnia, chronic pain, or psychological diagnoses. It is often quite difficult to be certain where the patient falls in this spectrum.

Rehabilitation of PCSs

Studies of early preventive interventions after mTBI show inconsistent results [308, 309]. There are some reports suggesting that an educational process improves the outcome in patients with mTBI [310–312]. An RCT found that a telephone intervention providing information about mTBI, assistance with strategies for managing symptoms, and resources in case of problems was associated with a reduction in symptoms at 6 months after injury compared with care as usual [313]. In a single-blind RCT of patients with TBI, mostly on the milder side, a telephone follow-up for advice and referral as needed 7–10 days following injury improved social disability and reduced PCSs compared with a control group with no specific intervention. Subgroup analysis demonstrated benefit only in those with length of PTA of less than 7 days [2, 314]. However, another study of patients with mTBI found no difference in PCSs at 1 year between those who received a telephone call or letter with advice and referral for rehabilitation as needed 2–8 weeks after injury and those with no intervention. In the intervention group, those with few PCSs declined rehabilitation and returned to work. Those with several PCSs accepted rehabilitation, but had not recovered after 1 year [315]. A single-blind RCT of all patients with mTBI presenting to the hospital found that there was no difference in the change in symptoms, community skills, or self-perception of general health among those who received rehabilitation interventions as needed vs. education (including that a good outcome could be expected) and advice [2, 316].

Although it may or may not prevent later symptoms, as with any disease process, patients should be educated about their illness. The patient can be told that dizziness, headaches, insomnia, cognitive impairment, and other PCSs are also likely to resolve overtime and that pain, emotional factors, and insomnia can exacerbate or cause cognitive impairment. If the symptoms, including cognitive problems, have been continuing for more than 10–14 days, it may be worthwhile to validate any anxiety that may be present by cautioning the patient that it is usually

stressful to experience these symptoms, especially cognitive dysfunction, and that this stress can itself further exacerbate the symptoms. Such education is as much an art as a science at this point in time.

When one suspects that an extended recovery is possible due to psychological issues, it may help to take it a step further and tell the patient that some people with PCSs experience a protracted course of recovery as a result of the stress involved and that if the recovery takes more than a few months, psychological issues are a possible cause and should be addressed in greater depth at that time. Having anticipated this process makes it easier to broach the subject of psychological issues at a later date, whereas patients can be otherwise quite resistant to accepting a psychological etiology for their symptoms. Having normalized the possible emergence of psychological problems will make it easier for patients to confront their anxious or depressive feelings and to accept treatment if they do occur.

Although it is probably the most commonly prescribed early intervention, there is little evidence that bed rest is helpful, and in fact it may be harmful [270, 317, 318]. Complete cessation of activity is almost impossible to adhere to and can result in anxiety, depression, and deconditioning. Patients should be encouraged to return to activities as tolerated, and follow-up should be scheduled in case of difficulty [270].

As noted above (see "Behavioral and Emotional Disorders"), cognitive behavioral therapy can be successful in treating anxiety and depression following TBI, including mTBI [319]. Symptoms such as dizziness may be influenced by cognitive behavioral therapy [320]. A study of individual cognitive behavioral psychotherapy combined with cognitive remediation in participants with persistent PCSs found that those in the experimental group showed better emotional functioning and also did better on a measure of divided attention than a waitlist control group [321]. Although not yet studied in mTBI, contextual behavior therapy and acceptance and commitment therapy are preferred by one group [262, 283]. As noted (see "Behavioral and Emotional Disorders"), if pharmacological intervention becomes necessary, depression is best treated with the SSRIs and the non-sedating SNRIs. Anxiety can be treated with these medications as well. However, a meta-analysis of controlled trials of both pharmacologic and non-pharmacologic interventions for depression following mTBI found that in fact, overall, controls did significantly better than the experimental groups [322].

If cognitive symptoms do persist, patients may benefit from cognitive rehabilitation to learn strategies for managing problems with arousal, attention, memory, and executive function (see "Cognitive Rehabilitation"). There is no published data to assist the clinician in determining if and when it is best to begin these interventions in people with mTBI, and there are no specific guidelines available. Clinicians must be careful not to contribute to some patients' exaggerated belief that the full extent of their cognitive problems is caused by brain injury [262]. Therapies should address the functional tasks that the individual is involved in in everyday life and may need to include community outings. Pharmacological interventions can be helpful (see "Cognitive Rehabilitation"), and again there is no information available on the timing of such treatment. Foam earplugs and sunglasses can be tried for those sensitive to noise and light, respectively [323]. When sleep apnea is contributing to attention or arousal problems, positive airway pressure therapy or a custom oral device designed to open the airway is indicated. Insomnia is also a common contributor to cognitive symptoms following mTBI. See Chap. 7 for a discussion of sleep disorders following TBI. Endocrine dysfunction should also be addressed if present. See Chap. 11 for a discussion of endocrine disorders after TBI.

As noted above, if PCSs persist beyond a few months, psychological intervention may be indicated, whether for assistance with reactive depression and anxiety or for preexisting issues. Instruction on sleep hygiene should be given for those with insomnia. Relaxation techniques can be helpful as well. Clinicians should continue to educate the patient and significant others with respect to the interaction between the cognitive, psychological, and physical sequelae. Support

groups are often useful. Family counseling is indicated when there is evidence of stress on family members or dysfunctional family dynamics.

There are several common types of posttraumatic headaches, and in any given individual, more than one can be at play [273, 324–327]. They should, therefore, be addressed on multiple levels, with the emphasis depending on the headache type. When patients have tension headaches, treating problems with attention, sleep disorders, and psychological stresses may reduce symptoms. Patients with myofascial pain originating in the neck, upper back, or temporomandibular (TMJ) joints generally benefit from physical therapy, including stretching and strengthening exercises; postural retraining; trigger point massage; modalities such as heat or cold (some respond better to one or the other) or electrical stimulation; electromyographic biofeedback; or massage. A workplace or other environmental evaluations can identify remediable factors that may be contributing. Trigger point injections can be helpful, as can systemic pharmacological approaches (e.g., some antidepressants, gabapentin, milnacipran – all "off-label"). Patients with TMJ problems can be treated with myofascial techniques, mouth guards, and exercises. Those headaches with an apparent vascular component (e.g., migraine headaches) may respond to acetaminophen, NSAIDs, or vasoconstrictive agents commonly used to abort migraine headaches (e.g., sumatriptan); but overreliance on these agents can cause medication overuse headaches (MOH) ("rebound headaches"). Patients must be educated about MOH and told to restrict the use of such drugs for the worst headaches if they are frequent. For prophylaxis, some beta-blockers (e.g., propranolol), calcium channel blockers (e.g., verapamil), antidepressants (e.g., amitriptyline, nortriptyline, venlafaxine), and anticonvulsants (e.g., valproic acid, gabapentin, topiramate) can be helpful (all "off-label"). Topiramate may be the most effective medication for prevention of migraine headaches, though it should be used cautiously due to its propensity to cause cognitive problems (see "Pharmacological Treatment of Cognitive Disorders"). Tension headaches may respond to some of these agents as well, though not to calcium channel blockers. Injection of local anesthetics and/or corticosteroids can be considered for greater or lesser occipital neuralgia that does not respond to more conservative approaches. Injection should be done at the site along the nerve that replicates the headache when palpated [325, 326, 328]. Botulinum toxin injections into pericranial musculature can be used for migraine prophylaxis, though may have only marginal benefit [329]. There may also be a role for botulinum toxin injections as prophylaxis against rebound headaches ("off-label") [330]. See Chap. 9 for further discussion of the treatment of headaches following TBI.

Dizziness following mTBI is often of the vertiginous type, with sensations of spinning or, more commonly, movement. Repositioning maneuvers can provide relief from benign paroxysmal positional vertigo by displacing and dispersing canaliths [331, 332]. When vertiginous dizziness persists beyond 3 months, exercise-based vestibular rehabilitation can bring about CNS accommodation under controlled circumstances, thus reducing symptoms [331]. The therapist can also instruct the patient in learning compensatory strategies when accommodation is not successful [333]. Cervicogenic dizziness is addressed by treating the underlying cervical musculoskeletal dysfunction. Suppressive medications (e.g., clonazepam, scopolamine, meclizine, gabapentin), if used at all, should only be tried when other approaches have failed [334]. The evidence for their efficacy is extremely limited, and some of them can cause an exacerbation of problems with attention and memory. Occasionally perilymph fistula is the cause of persistent vertigo, but the diagnosis is difficult to make. Pressure-induced vertigo or disequilibrium and sensorineural hearing loss are often present. The outcomes with respect to vertigo are reported to be good in 82–95% of cases, but only case series have been published. Recurrence rates are reported at 8–27%, but others believe the recurrence rate is considerably higher, as much as 67% [335–339]. See Chap. 8 for further discussion of vestibular disorders.

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Interventions to Improve Cognitive Functioning After Traumatic Brain Injury (TBI)

Anthony Chen, Tatjana Novakovic-Agopian, and Fred Loya

Introduction and Overview

Case

A service member returning from active duty deployment to the Middle East states that he was exposed to multiple blasts in combat. In one incident, while he was riding in a convoy, his truck was struck by a blast from a roadside improvised explosive device. A wheel was caught in the crater and the vehicle dove into a ditch. "I think my head struck the side of the truck, and I may have blacked out—I'm not sure how long." He admits to feeling dazed and somewhat confused. This seemed to resolve within a day, and the soldier returned to full duty. However, he was exposed to several more blasts during his deployment. While he cannot recall the details of each incident clearly, he endorses feeling dazed with each episode. He complains that he has had many difficulties since returning home. He has had trouble getting organized for job applications and other tasks—"I would get started, but then I always ended up doing something else." He complains of feeling highly distractible and easily overwhelmed and states that his memory is like "swiss cheese." Others describe him as irritable and easily angered. He has difficulty in sleeping, feels depressed, and avoids leaving his home.

Cognitive Dysfunction from Traumatic Brain Injury

This individual's experience is quite common among veterans who have served on active duty. Recent combat-related activities in the Middle East have resulted in an increased incidence of TBI among military personnel. The rate of TBI-related military hospitalizations increased by 105% between 2000 and 2006 [1], and over 350,000 servicemen and women have been diagnosed with a TBI since 2000 [2]. Moreover, it is estimated that one in five service members of the conflicts in Iraq and Afghanistan sustained a TBI during combat operations [3] and that nearly 60% of those exposed to blasts incurred some form of closed head injury [4]. Although the majority of these military-related injuries can be classified as "mild," their long-term consequences are often far-reaching and multiple. One study of medical records at a United States Department of Veterans Affairs (VA) Medical

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Center Polytrauma clinic found that nearly 70% of veterans reported persistent post-concussive symptoms [5], defined as symptoms lasting 3 months or longer, following their initial injury. Of note, this symptom profile differs considerably from the typical recovery trajectory [6]. For these reasons, TBI is considered the "signature injury" of the conflicts in Iraq and Afghanistan [7].

From Acute to Chronic Cognitive Dysfunction

In an instant, an injury to the brain can cause changes that affect a person for a lifetime. Although the injuries are acute, functional deficits that result from TBI may produce tremendous *chronic* burden on individuals, families, and health-care systems. This discussion will focus on problems that persist to become debilitating on a chronic basis. This is an important area to address for several reasons. The intrinsic importance of problems that are persistent (not resolving spontaneously or not responsive to therapies) is obvious. Acquired brain injuries have been a leading cause of long-term disability in the USA even before the current conflicts [8] and a leading contributor to increasing health-care costs in the VA health-care system [9]. Individuals with TBI are at risk for being unable to live independently. Surveillance for TBI across 14 states showed that approximately one-third of patients continue to require assistance with daily activities 1 year after injury [10]. For patients hospitalized for TBI, cognitive status is a major factor in determining whether individuals are to be discharged from institutions [11]. Long-term consequences of TBI frequently include impaired cognitive functions involving attention, executive abilities, and learning and memory as well as emotional volatility and increased incidences of psychiatric comorbidities [12–14]. A more dire but difficult to quantify consequence is the cascade that may lead to poor community outcomes, including joblessness, homelessness, additional poor health outcomes, and even suicide [15–17].

For less severe dysfunction, patients may have symptoms that are not readily recognized by health-care providers but which are significant and need to be addressed [18]. One specific challenge for combat-related injury is that some of the "milder" effects of brain injury may not be immediately detected. Detection may be particularly complicated as some individuals experience problems that only become apparent with a change in setting, new cognitive demands, loss of supportive social structure, and demands to learn new skills or knowledge. For example, cognitive dysfunction may become particularly debilitating during transitions from the familiar structure of military life to civilian life, including adjustments to school or new occupations.

TBI, if recognized at all, is predominantly addressed during acute stages. Ironically, *chronic* cognitive problems tend to receive relatively little medical attention. The issue of insurance coverage in the private sector has been raised as one barrier to care that has even been recognized by the public press [19]. However, another fundamental factor is the need for improved guidance for treating chronic cognitive dysfunction. Treatment needs tend to be complex and individualized, and few general guidelines have been available to guide treatment. However, an evidence base for cognitive rehabilitation interventions is being progressively strengthened. For military veterans, access to care has improved significantly in the past decade.

A long-term view is needed and major long-term issues need to be taken into account in clinical programs [20]. The far-reaching impact of these seemingly "invisible" deficits is often not recognized. For example, individuals who cannot pay attention, hold information in mind, and actively participate in learning activities will have reduced benefit from other rehabilitation efforts, such as those directed toward motor or speech functions [21]. Individuals who have suffered a TBI may also be at increased risk for developing cognitive changes later in life [22–26].

Injuries and Cognitive Symptoms

Although it is commonly understood that TBI can result in almost any neurologic deficit, the most

common and persistent deficits tend to be in cognitive functions. Among cortical regions, prefrontal and mesial temporal structures are vulnerable to contusions and hemorrhages. These correspond to deficits in frontal executive functions and declarative memory, as well as other aspects of behavioral and emotional self-regulation. Diffuse or multifocal axonal injury may affect commissural, callosal, and association as well as particularly vulnerable long fibers, including those carrying neuromodulators in projections from the brainstem to cerebral end targets and those that connect the prefrontal cortex (PFC) with other brain regions. Some of the most common deficits with distributed axonal injury, even in the absence of cortical lesions, are in speed of processing, frontal executive functions, and memory [27]. The nature of cognitive dysfunction with TBI and intervention approaches for these symptoms are discussed in greater detail in this chapter.

Are cognitive deficits important in mild TBI (mTBI)? The occurrence of cognitive deficits in moderate and severe TBI is well-recognized, but cognitive deficits may also be a significant problem after so-called "mild" TBI [6, 13, 28–32]. Delineation of cognitive dysfunction has been more problematic, however. The controversies and debates have been extensive. Recent data from systematic tracking of individuals with mild TBI in both civilian and military settings are consistent with clinical observations that a significant number of individuals continue to have symptoms months to years after injury [33, 34]. We argue that it is particularly important to define the severity of dysfunction, rather than relying on a gross grading of initial injury severity. It is clear that traditional labels of "mild, moderate, or severe" are poor characterizations of individuals with TBI [35]. Furthermore, injury history is often not clear for many veterans who suffered injury(ies) in the field, making these labels even more imprecise. Current functional status is measurable. For the current discussion, an emphasis is placed on considering persistent "mild" cognitive dysfunction. Although self-reported symptoms and outcomes from cognitive testing vary greatly, deficits in control processes, including attention and working memory, and speed of information processing are commonly reported and may be the most affected domains in mTBI [6, 13, 28–32]. Aspects of executive control may be important factors in determining successful return to work after mTBI [36].

Spontaneous recovery? Despite their importance, chronic deficits in cognitive functions are often poorly addressed. Advice that recovery will occur with time can be reassuring, and, fortunately, the recovery trajectory for most patients who survive TBI is positive over time. However, there is significant variability in the rate and end point of recovery. A significant minority (10–20% of those with "mild" TBI, in nonmilitary settings) report persistent deficits that can last months and years post-injury, leaving chronic, residual disabilities that have a wide-ranging impact on an individual's life [28, 37]. Persistence of symptoms after combat neurotrauma is worth special consideration. As will be discussed in this chapter, there may be a number of contributors to poor cognitive functioning, aside from the physical brain injury per se.

Approaching treatment of post-TBI cognitive dysfunction is complicated by the frequent occurrence of multiple and varied symptoms. For example, the existence of a "post-concussive syndrome" (PCS) is now widely accepted, though this remains a somewhat difficult to define entity or entities, with variable presentations, sources, and possible courses. The syndrome may be characterized by headaches, dizziness, general malaise, excessive fatigue, and/or noise intolerance; irritability, emotional lability, depression, and/or anxiety; subjective complaints of concentration and/or memory difficulties; insomnia; reduced tolerance to alcohol; preoccupation with these symptoms; and fear of permanent brain damage. Documentation of cognitive dysfunction on "objective" testing is not required for diagnosis even though cognitive symptoms are common.

Although these symptoms, by definition, occur after a concussion, this does not necessarily mean that brain injury directly causes these symptoms. Multiple factors may contribute to or "modulate" symptoms. This is a particularly important consideration given the contexts in which physical trauma and recovery periods

occur, including the associated traumatic experiences in combat or even in medical settings. These factors may be important in formulating interventions to improve functioning.

A Combined Combat Neurotrauma Syndrome

It is increasingly recognized that a large portion of individuals returning from combat activities suffer from both TBI and post-traumatic stress (PTS) symptoms or even the full disorder (PTSD). A 2005 survey of Iraq/Afghanistan veterans found that for the 12% of 2235 respondents with a history of mTBI, the strongest factor associated with persistent post-concussive symptoms was PTSD, even after removing overlapping symptoms from the PTSD score [38]. A cross-sectional survey of Army veterans, 3–4 months after return from Iraq in 2006, revealed the highest prevalence of PTSD among those with a history of loss of consciousness (LOC) [7]. LOC was also associated with major depression. mTBI (defined by a history of traumatically induced disruption of brain function accompanied by LOC or alteration of mental status) was associated with post-concussive symptoms—but not after controlling for PTSD and depression. In examining the incidence of PTSD, rates increase in relationship to the occurrence of TBI, with increased incidence of PTSD along the gradient of no TBI to altered mental status to LOC [39]. Veterans with history of mTBI are two to three times more likely to demonstrate significant PTSD symptoms than those with no brain injury [38, 40]. A 1.5- to 2.7-fold magnitude increase in PTSD risk associated with history of mTBI has been observed in active duty service members [41–44]. PTSD diagnosis and symptoms and persistent post-concussive symptoms are more common among those reporting mTBI with LOC as compared to those with mTBI without LOC [7, 45, 46]. A study examining TBI and PTSD service utilization of OIF veterans found that 1-year post-deployment, 65% of those with mTBI–PTSD reported seeking treatment for concerns related to re-integration [47]. Observation suggests that the combination of TBI with PTSD may result in more prolonged or more complicated courses of recovery. All of these epidemiological findings raise questions about the interactions between TBI and PTSD.

The interactions between TBI and PTSD are undoubtedly complex and multilayered. Trauma may alter an individual's brain functioning via many routes. Direct physical injury may certainly be caused by traumatic forces, leading not only to contusions, hemorrhages, and even strokes but also injuries to the white matter fibers that connect brain regions. However, severe distress from the traumatic experience may also have immediate as well as long-term effects on brain functioning. Post-traumatic stress effects are increasingly recognized as being mediated by altered brain functions and possibly structure. Both physical and experiential trauma may contribute to acute disruption of function as well as ongoing cascades of sequelae that layer upon the initial injury. Understanding that these mechanisms of injury interact at multiple levels is of great importance for understanding, diagnosing, and managing the effects of these injuries. This may have particularly important ramifications for the formulation of interventions, and this is discussed in detail in this chapter.

The story told by the veteran above is likely to raise a number of important questions in a clinician's mind, including questions of etiology, diagnosis, and diagnostics, but perhaps the most important question is this: What can be done to improve this person's functioning?

Approaches to Intervention

Synopsis of Intervening to Improve Cognitive Functioning

The following are key points to consider in determining interventions for improving cognitive functioning after brain injury:

- The most common difficulties after TBI involve complex attention, learning, memory, organization, and other processes important for goal-directed behavior.

- Sources of dysfunction may be multifactorial, and each factor or interaction of factors represents a potential target for intervention. Sources include not only deficits in specific neural processes but also functional difficulties in engaging cognitive processes for goal-relevant activities, factors that modulate physiologic brain states, emotional factors that interact with cognitive functioning, pharmacologic and other biological modifiers, and interactions of cognition with specific environments. The interactive nature of these factors is illustrated in the overlapping layers in Fig. 1. Any or all of the above may have to be taken into account for a therapeutic intervention to be effective. Each of these layers is discussed in this chapter.
- Interventions may be targeted to specific cognitive processes, specific sources of dysfunction, supportive processes, specific modulating or exacerbating factors, and/or an integrated approach that addresses multiple targets concurrently based on a particular therapeutic goal.
- Some processes may be worth targeting even if "deficits" are not detectable. This includes, especially, domain-general processes that are "gateways" to learning and change. A core set of cognitive processes may be considered central to enhancing the rehabilitation process itself. These include "meta-cognitive" processes such as self-awareness (awareness of one's abilities, strengths, weaknesses, and goals, with the ability to monitor and review one's actions in these contexts) and functions

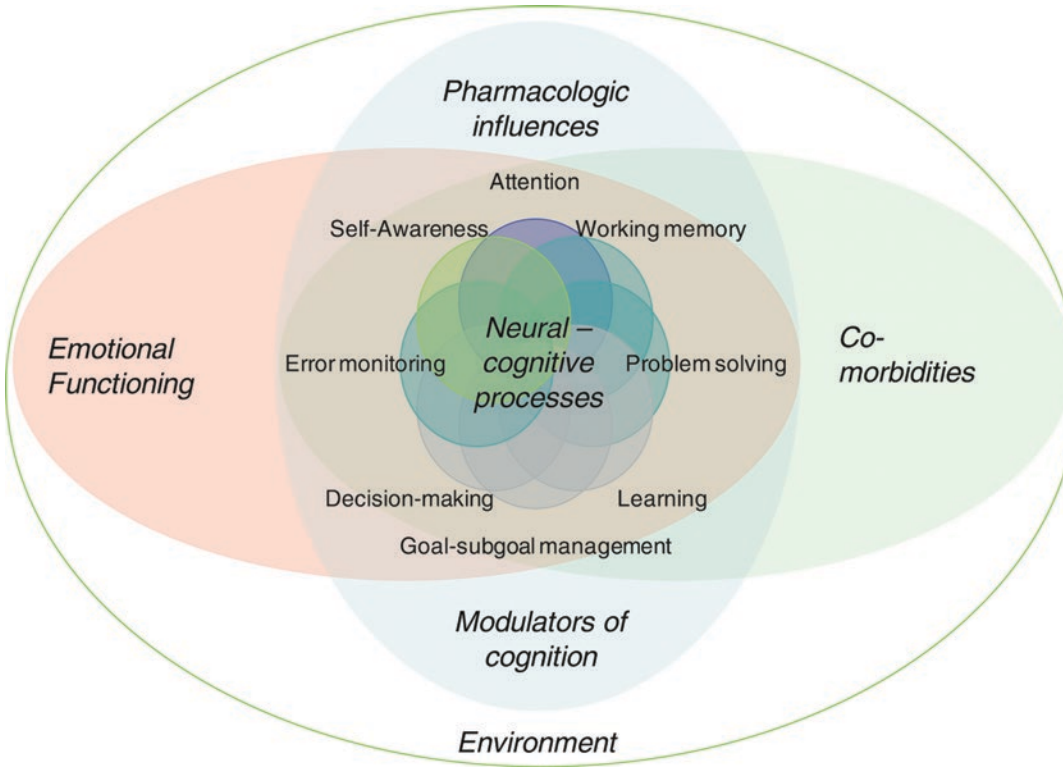

Fig. 1 Multiple sources of dysfunction lead to multiple tiers of intervention. Core targets of intervention include specific neural–cognitive processes important for healthy, goal-directed functioning after brain injuries. However, these processes may also be affected by modulators that alter cognitive state or cognitive performance (e.g., sleep, fatigue), pharmacologic influences (e.g., medications, other drugs), emotional functioning (e.g., irritability, anger, depression), and other comorbidities (e.g., chronic pain). All of these are potential targets for interventions to improve cognitive functioning

for regulating attention, learning, and memory in an organized, goal-directed manner. These processes will also be crucial for continued learning and adaption outside of clinician-guided settings.

- Underlying cognitive and emotional functioning are aspects of brain state, so addressing the fundamental ability to regulate one's state may have a far-reaching impact.
- Approaches for modifying behavior include training, i.e., the guidance of learning through activities with specific learning goals. Training forms the most fundamental core of post-injury rehabilitation but may be combined with approaches that optimize biology and other modulators to maximize benefit.
- A number of factors may need to be accounted for in synergizing therapies to optimize improvements in functioning. These include understanding not only the immediate effects of pharmacologic agents but also the potential influences on processes of learning and change and relationships between the underlying neural systems modified by these agents vs. training. Different drugs, as well as different doses of the same drug, may have differential effects for specific neural subsystems and the behaviors they subserve.
- Engagement of active participation for each individual in treatment is a major factor in treatment outcome. Elements of enhancing engagement include raising awareness of one's abilities and difficulties, opportunities for self-direction during treatment, and active attempts at applying and transferring learned skills to personally relevant situations and goals. These considerations become all the more important when deficits affect awareness, motivation, attention, and other aspects of self-regulation. Issues of active avoidance or negative reactions to intervention may be further heightened when TBI is combined with PTSD or other psychological health conditions.
- Transfer of gains to new contexts and generalization to each individual's personal life must be taken into account when considering intervention approaches as well as measurement of outcomes.

Overarching Considerations in Intervening to Improve Cognitive Functioning After Brain Injury

Interventions may be considered along a number of major axes. Each of these axes briefly highlights particular considerations in determining optimal interventions, discussed briefly in this overview and in more detail in subsequent sections. Considering the spectrum along each axis may be helpful in determining the best approach for each patient.

Targeting the Environment vs. the Patient Managing an individual's environment (organization of the physical environment, work, time demands, etc.) is a common approach to post-injury care. This may be particularly valuable during acute phases of injury or with more severe deficits in self-management. This approach may sometimes be taken alone for at least two reasons. First, there may be an interest in maximizing function in a specific environment, given the least amount of time and effort. Second, there may be an assumption that the patient's functioning is "static." However, there may be significant functional plasticity over long periods of time, even if the time course is not always in line with standard practice parameters. This chapter focuses more on patient-targeted approaches, where one of the ultimate goals is to alter the abilities of an individual to adapt to or manage their own environment.

Targeting of Ancillary Health Factors vs. Directly Targeting Central Neural–Cognitive Processes A number of ancillary factors may be addressed that may have dramatic effects on cognitive functioning. Addressing these contributing factors may reveal a clearer picture of the underlying status of an individual's cognitive functioning and may complement approaches targeted at improving core functioning.

Application of External Tools vs. Internalized Skills and Strategies Within an individual's "personal environment," one may consider external tools vs. internal tools available for a patient's use. The use of external tools is clearly a valuable

aspect of human functioning and has an important role in improving functioning post-injury. Strong evidence supports the use of external tools for improving an individual's ability to accomplish intended actions. Tools may provide immediate benefits as external "signals" or orthotics (e.g., paging systems for alerts or reminders [48, 49]), but they may also include training to leverage external tools to compensate for one's deficits or augment one's abilities (e.g., using a planner to improve organizational skills). An important question for continued investigation is the extent to which any tools may improve an individual's intrinsic abilities. In this chapter, we focus on approaches that may alter an individual's functioning via internalized skills and strategies.

Behavioral Modification vs. Biological Modulation Methods for modifying biological underpinnings of behavior may be applied separately or in combination with behavioral modification. Biological modification approaches may include not only pharmacotherapy but also identification and targeting of factors that influence the neural systems that support cognition. These may include factors, such as sleep, pain, physical activity, circadian systems, nutrition, and more. It is valuable to keep in mind that biological approaches will more likely aid in accomplishing therapeutic goals when applied in the context of a behavioral modification plan (e.g., goal-driven rehabilitation training), rather than in isolation. Behavioral therapies may be more successful with strategic biological modulation—for example, learning capacity may improve with coordinated efforts to improve sleep, attention, and memory.

Factors That Modulate Cognitive Functioning and "Brain State" on a Dynamic Basis: Important Targets of Therapy

Medications

Integrating Pharmacotherapy with Rehabilitation Careful application of pharmacotherapy can play an important role in improving cognitive functioning after brain injury. Clinical evidence to support particular medications post-TBI is sparse but slowly accumulating (reviewed in [50]). A clinician's prescription for any given individual still relies on theory and/or empiric practice, informed by limited direct evidence or extrapolation from other populations. Systematic individual trials involving stepwise dose adjustments of medications may be helpful.

There are a number of reasons to consider neuromodulator systems of the brain as therapeutic targets. These include findings that TBI tends to affect cognitive functions dependent on these neuromodulators, such as dopamine, norepinephrine, acetylcholine, and serotonin, and the predilection for TBI to affect the cortical termination zones as well as the long projection fibers that carry these neuromodulators. Almost all of the major neuromodulators of the brain are produced in small nuclei at the base of the brain or in the brain stem and project to distributed cerebral structures. Acetylcholine from the basal forebrain is projected to cortex throughout the brain. Dopamine from the ventral tegmental area is projected primarily to PFC. Norepinephrine from the locus coeruleus is projected to cortex throughout the brain, as well as thalamus, cerebellum, and spinal cord. Serotonin (5-HT) is also predominantly produced in brainstem and rostral nuclei (in the pons and midbrain) projections throughout the brain, with prominent targets including frontal lobes and hippocampus. On the other hand, GABA neurons are distributed throughout the brain, in particular as inhibitory inter-neurons. Disruption in one or more of these systems presumably contributes to neurologic symptoms seen in TBI.

A number of drugs that affect neuromodulator systems have been used in clinical practice for years. Each pharmacotherapeutic agent is, in theory, targeted to particular neural systems, whether defined by particular receptor types, synthesis of or metabolism of particular neurotransmitters, or other drug-specific mechanisms. The delineation of the targets of a particular drug in relation to cognitive functioning is an area in need of further investigation.

Helpful and hurtful effects of drugs must be considered, and these may occur simultaneously. For example, more detailed examination may reveal domain-specific effects (as described in McDowell and coauthors [51]) or simultaneous helpful vs. detrimental effects on separable brain systems (i.e., "double-edged sword" effects) [52]. An important frontier will be to determine the pharmacology of each patient, potentially providing guidance for therapy.

It is also valuable to consider immediate vs. longer-term effects of pharmacologic modulation. Drug effects may be supportive for current issues, but may also be detrimental for longer-term goals. For example, anti-dopaminergic medications have long been used to address problematic behavior post-injury. The immediate effects may seem helpful (e.g., reducing behavioral instability), but the same medication may adversely affect functioning in a cumulative manner (e.g., by altering attention and learning during training). It is important to manage the goals, timing, and duration of therapy.

Patients may have prescriptions for issues that arise during the many phases from acute injury to chronic recovery. Polypharmacy is a common problem, likely due to factors such as multiple comorbidities with TBI (e.g., anxiety, PTSD, insomnia, pain) and attempts to treat some post-TBI sequelae (e.g., behavioral dysregulation, seizures, headaches). A valuable first step in clinical decision-making is a review of medications that may contribute to poor cognitive functioning. Unfortunately, numerous medications commonly used for patients with TBI have adverse effects on cognition or learning/plasticity.

Post-traumatic epilepsy, especially with complex partial seizures, is a treatable potential contributor to cognitive dysfunction. However, medications may need to be managed with attention to cognitive side effects. Phenytoin has been shown to impair cognitive function in patients with severe TBI [53, 54]. Carbamazepine may also have cognitive side effects [55]. Among older anti-epileptic agents, valproate may be preferable. Among newer agents, topiramate may be particularly concerning for cognitive side effects. Levetiracetam has fewer drug interactions, though it may contribute to mood/thought disturbances.

Benzodiazepines and baclofen are GABA agonists, and these may reduce the rate of recovery from TBI [56]. The use of these medications should be minimized in the context of cognitive dysfunction after TBI. In certain circumstances, spasticity may be treated by more localized means (e.g., intrathecal baclofen or targeted botulinum toxin). On the other hand, strategic and judicious use of beta blockers or benzodiazepines may improve cognitive functioning clouded by anxiety.

Dopamine antagonists, such as haloperidol, have been shown to impede learning and recovery [57–61]. These agents are commonly used for managing behavioral dysregulation, but should be used sparingly, and continual use should be avoided as much as possible. On the other hand, limited strategic use at night may improve sleep and daytime functioning, especially for some individuals with nightmares and anxiety related to PTSD.

Selective serotonin and/or norepinephrine reuptake inhibitors (SNRIs) may help reduce emotional lability and improve functioning, and although evidence is limited for TBI, this may be especially useful in the contexts of depressive or anxious symptoms.

In sum, it is important to repeatedly review the rationale, necessity, and dosage of each medication at each clinical juncture, with a concern for potential adverse effects on cognition and recovery. In general, when medications are deemed necessary, cognitive functioning should be monitored while dosing is adjusted. It is best to initiate pharmacotherapy in the context of a plan for non-pharmacologic treatment and to have clear rationale for how the pharmacotherapy will support the long-term goals of treatment along with plans to eventually taper or more selectively use pharmacotherapy. Discontinuing certain medications can be as valuable as starting any medications in the rehabilitation course.

Alertness and Arousal State

Optimal arousal state may be considered a prerequisite for effectively activating and engaging

other cognitive functions. The concept of alertness is integrally tied to the sustainment of attention. The translation of alertness or arousal to task-related attention may lead to greater neural–cognitive processing [62]. Tonic alertness refers to the ongoing state of intrinsic arousal that is intimately involved in sustaining engagement during higher-order functions, such as selective attention, working memory, and executive control [63, 64]. Although the term "attention" is commonly used in this context, it should be distinguished from the many other meanings of attention, as separable neural systems appear to subserve alertness vs. other "attention" functions [63, 64]. Alertness may influence performance in almost all cognitive domains, including during rehabilitation [62–64]. Improving regulation of this "gateway" function may improve an individual's "readiness" to participate in rehabilitation.

Regulation of arousal state needs to be considered in terms of optimizing balance for any given goal or context. Patients with more severe TBI may exhibit marked deficits in alertness [65, 66]. Noradrenergic systems involving inter-connected regions of brainstem and frontal cortex, in particular, have been proposed to be particularly important mediators of alertness state [67]. The importance of long distance connections, both for delivering noradrenergic signals from brainstem to cortex as well as regulation of brainstem nuclei, may help to explain why alertness is so often dysregulated after TBI. High levels of arousal may also be maladaptive. This is a significant problem with TBI–PTSD, for example. Thus, therapies may need to focus on the concept of optimizing the *regulation* of alertness, rather than simply increasing or decreasing arousal per se.

Approaches to regulating arousal state may involve behavioral regulation, training, and pharmacologic treatments. Recent training approaches may provide methods for improving regulation of arousal and are discussed in more detail with other training approaches. A number of pharmacologic agents that affect alertness and arousal are already in common use. However, the effects of each agent can be quite individual, especially given underlying issues with variability in alertness state, i.e., lability, rather than a simple unidirectional deficit. Thus, each agent needs to be considered carefully based on patient goals and treatment contexts. Multifactorial considerations become particularly challenging when TBI is combined with post-traumatic stress symptoms, behavioral lability, anxiety, or depression.

Commonly used pharmacologic agents that affect neuromodulator function include methylphenidate and amphetamines as well as newer stimulants. For example, methylphenidate has been shown to alter sustained attention in patients with TBI [68]. Modafinil is a newer agent that promotes alertness. Atomoxetine works selectively on noradrenergic systems. "Antidepressants" with noradrenergic targets and possible "activating" effects, such as venlafaxine or duloxetine, may be helpful for some individuals. These agents could be considered for use as agents satisfying multiple therapeutic goals, minimizing the total number of different medications. Reuptake inhibitors for serotonin as well as norepinephrine are perhaps among the few agents that may improve stability of arousal state.

As always, the effects of medications prescribed for other reasons must be evaluated. Other factors that modulate cognitive state that are related to alertness are fatigue and sleep. These are discussed separately, given some distinct considerations.

Energy and Post-Injury Central Fatigue

Adequate energy is required to drive cognition and behavior, particularly for the effortful pursuit of higher-order goals, learning, adapting, and problem-solving in the context of challenges after brain injury. However, fatigue is reported to be one of the most common and debilitating symptoms after TBI [69, 70]. There is no standard definition of fatigue, but key elements include a requirement for increased effort to maintain mental activities and difficulty sustaining goal-directed efforts [71]. Central fatigue, related to disturbance in the CNS, is itself a major cause of poor functioning and can adversely impact recovery efforts, emotional well-being,

cognitive functioning, quality of life, and one's ability to perform daily activities [72, 73]. Fatigue can manifest as difficulties with concentration, feelings of being overwhelmed, and/or lack of perseverance with tasks that feel too effortful. Helping an injured individual to manage available energy, including increasing available energy for key goals, would be of great benefit for optimizing current functioning and encouraging learning for longer-term improvements.

When assessing fatigue, it is critical to take into account its dynamic nature, noting how it fluctuates over time and in the various contexts in which an individual functions. A key goal is determining potential contributing factors that may serve as direct targets for clinical management, including through assessing associated factors, such as sleep, depression, and pain [74, 75]. From a clinical best practice perspective, regular physical exercise, which has shown to reduce fatigue in other clinical populations [71, 76], is a front-line treatment option. Factors such as poor motivation, chronic pain, and other physical limitations may need to be addressed to help patients fully engage in this form of treatment. Overcoming these problems may require creative problem-solving, with guidance in individualizing exercise activities.

Compensatory strategies to manage energy use, such as setting restrictions on the length of time to engage in certain activities, may also be helpful. This behavioral approach involves identifying personal and/or situational factors associated with fatigue and then developing strategies for managing or modifying these factors in order to minimize energy loss. One potential complication of this approach may stem from the decreased awareness of persons with brain injury to accurately identify and observe these factors. Patients may require repeated assistance and scaffolding to identify potentially modifiable situations or behaviors that contribute to fatigue, as well as support in implementing strategies in personal life.

Reducing distractions and thereby minimizing the amount of cognitive effort required to accomplish tasks may also be beneficial. Improved self-regulation of attention and other aspects of cognitive processing may help improve cognitive efficiency. Similarly, improving regulation of emotions, such as anger, may also be required. There is some preliminary support for the use of mindfulness-based stress reduction (MBSR) to reduce fatigue. Studies incorporating MBSR principles have found reductions in mental fatigue for persons with TBI or stroke [77] and increased self-reported energy at 1-year follow-up [78]. Such findings are cause for optimism, as they suggest that non-pharmacological, state-based approaches have great clinical potential. A review of medications is important, as beta blockers, anti-dopaminergic agents, and anti-epileptic drugs may all contribute to feelings of tiredness. Pharmacotherapy with agents that improve alertness, attention, and concentration, such as methylphenidate, amantadine, dextroamphetamine, atomoxetine, or modafinil, as well as activating antidepressants may also be helpful. Research has shown that these agents confer benefit for persons experiencing illnesses where fatigue is a common feature [79–82]. Preliminary findings of medication trials to treat fatigue within the context of TBI have been mixed [83], and more research is clearly needed to ascertain specific medication effects. The use of pharmacotherapy timed to augment participation in other therapies remains a major frontier for development with potentially wide-reaching benefits for individuals with brain injury. The development of objective measures of fatigue may be particularly helpful for identifying underlying causes of fatigue. Potential neural correlates of fatigue in persons with TBI and other forms of brain injury have been explored using functional MRI (fMRI) [84, 85], with findings of increased activity in multiple brain areas suggesting compensatory recruitment of neural resources not required of uninjured persons [86]. Elucidating the underlying biology of fatigue may have important implications for further management approaches.

Sleep

Sleep disturbance is one of the most common, yet least studied, sequela of TBI [87–90]. Recent research estimates that up to 84% of persons with a TBI experience some form of sleep disturbance

[5], with symptoms of insomnia being the most frequent complaint [91]. Sleep difficulties may arise from multiple sources, including the direct effects of alterations to brain chemistry [92, 93] or secondarily to comorbidities, such as anxiety and depression or chronic pain [94, 95] that frequently occur within the context of mild to moderate TBI. Consequently, clarifying the complex web of potential factors contributing to sleep disturbance represents an important clinical goal, with direct implications for the development of therapeutic interventions targeting multiple potential levels. The neurocognitive, behavioral, and physiological effects of poor sleep within the general population have been well documented [96, 97]. Within TBI populations, specifically, sleep disturbance has been shown to exacerbate deficits in sustained attention [98] and may also contribute to worse rehabilitative outcomes [99] and quality of life [100]. Importantly, several studies [95, 101–103] have documented that sleep disturbance persists in many persons with mild to moderate TBI for several years post-injury, underscoring the importance of addressing this potential chronic sequela of brain injury.

More broadly, sleep regulation and adequate sleep may be of fundamental importance for learning and recovery after brain injury. Sleep deprivation may adversely affect functions crucial for learning, such as alertness, sustained attention [98], and other forms of attention and memory, with particular adverse effects on frontal system functions [88, 104, 105]. Chronic lack of sleep may also be associated with anxiety and depression [106].

From another perspective, sleep, including in the form of brief naps, has been shown to benefit learning of information or skills learned prior to sleeping [107, 108], even in the absence of REM sleep [109]. Thus, promoting sleep as a prospective intervention (i.e., encouraging sleep after learning) may be a valuable component of rehabilitation.

Despite the importance of sleep for optimizing functioning and enhancing learning after TBI, no strong evidence base exists to guide clinical best practice [103, 110]. However, there are a number of clinically useful options available. The most basic considerations include recommendations for sleep hygiene, including limiting the use of substances (e.g., caffeine, alcohol, or other drugs) known to adversely affect sleep, stimulus control, sleep restriction, and relaxation techniques. One recent study found that educating nursing staff was critical in helping to change behaviors supportive of proper sleep in a hospital setting [111]. For many individuals, there may be opportunities for improving functioning in just addressing basic aspects of sleep hygiene.

Pharmacologic agents for inducing or prolonging sleep all have potential side effects, and balancing effects become more complex when cognitive dysfunction and other medications, among other factors, inter-mix. Furthermore, medication-induced sleep does not replace normal physiologic sleep. Benzodiazepines and atypical GABA agonists, some of the most commonly used sleep agents, may have adverse effects on cognition and neuroplasticity following injury as well as rebound effects [112]. Judicious short-term use can be beneficial in limited situations (e.g., when overwhelming anxiety contributes to insomnia), but rapid tolerance and dependence can make management difficult. Other agents, such as trazodone, or newer antidepressants, such as mirtazapine, may have clinical utility, although there are few data to guide their use after TBI. Individuals with TBI may have increased sensitivity to adverse effects, such as prolonged cognitive effects the next day, so, in general, low doses or slow titrations may be particularly important.

Sleep-supportive agents may play an important short-term role during rehabilitation. For example, such drugs may be used during initial phases of therapy, to temporarily address extreme sleep deprivation and associated complications of cognitive and emotional dysfunction that may impede initiation of other therapies with longer-term benefits. Use of such drugs would ideally be limited in time, matched with non-pharmacologic therapies with the goal of eventually improving sleep management and tapering off medications.

Non-pharmacological therapies aimed at addressing psychological factors thought to perpetuate sleep disturbance have shown great

potential. One particularly promising treatment is Cognitive Behavioral Therapy for Insomnia (CBT-I). In general, cognitive–behavioral therapy is based upon the premise that feelings and behaviors are driven by underlying thoughts. Thus, in therapy, a primary task is changing unhelpful patterns of thinking as a means of bringing about behavioral change and improving one's overall well-being. CBT-I both addresses unhelpful cognitions associated with insomnia (e.g., addressing maladaptive sleep-related beliefs) and utilizes behavioral techniques (e.g., stimulus control). Meta-analytic findings [113, 114] indicate this approach is as efficacious as pharmacotherapy in the short term and potentially more effective in the long run. There is some suggestive evidence that this treatment approach may be beneficial for persons with TBI. Ouellet and Morin [115, 116] reported positive results, including polysomnographic changes, following CBT-I in persons with TBI of varying severity, providing some preliminary indication that this may be a helpful treatment.

There is also some suggestive evidence that treatments targeting the regulation of the circadian rhythm and sleep-wake cycle are effective in the context of TBI-related sleep disturbance. Disruption to the production or synthesis of melatonin, a hormone involved in the regulation of the sleep-wake cycle, following brain injury has been posited to be one mechanism through which sleep disturbance occurs following TBI [117]. Exogenous melatonin therapies have been shown to result in modest benefits in sleep-related outcomes in non-TBI populations [118, 119], and preliminary findings suggest it may be helpful in the context of TBI [120]. Others [75] have also suggested that light therapy may be a beneficial treatment approach given its effectiveness in treating a broad range of sleep pathologies [121]. Intensive schedule regularization in combination with efforts to augment sleep or wake signaling (e.g., melatonin supplementation at night, sunlight, exercise, and possibly stimulants in the morning) may also be valuable.

Identifying and treating sleep apnea is another major priority for persons with TBI. Sleep apnea has been shown to contribute to cognitive dysfunction via both disruptions of the regular sleep cycle and potentially from hypoxia itself [122, 123]. Caution should be exercised regarding prescription of sleep-inducing medications, such as benzodiazepines, within this context as they may actually exacerbate apnea. Traditional treatment via a CPAP machine has been shown to be helpful for obstructive sleep apnea following TBI [124].

Management of sleep as a direct, explicit target of therapy is an important frontier for further development. There remains a major need for defining optimal approaches for improving sleep duration and quality after TBI, as well as determining how best to integrate sleep into rehabilitation treatment regimens. Successful improvement of sleep will have far-reaching benefits for individuals with TBI and neuro-behavioral dysfunction, especially as they work through other modalities to improve functioning.

Pain

Pain is a common accompaniment of TBI. Chronic pain, in particular, may have wide-ranging effects on well-being, emotional and social functioning as well as cognitive functioning. Although detailed consideration is beyond the scope of this chapter, there are some general principles worth considering in the context of optimizing functioning. Some of the effects of pain on cognition may be mediated by influences on sleep, mood, and energy levels. For example, chronic pain may lead to irritability and poor frustration tolerance, reducing cognitive effort for cognitive tasks that are challenging. Pain may also modulate cognitive functioning via increased fatigue or poor sleep. On the other hand, treatments for chronic pain, such as with opioid analgesics, may contribute to poor cognitive functioning. Although opioid medications may play an important role in pain management, especially in settings of acute injury, other approaches may be particularly valuable in the long term.

Multidisciplinary collaboration in an intensive program may be necessary, especially given the multifactorial nature of chronic pain. Approaches to pain management that include strengthening of self-regulation and coping

(e.g., with mindfulness-based training or biofeedback), as well as localized interventions (e.g., transcutaneous electrical stimulation, injections), with a goal of minimizing systemic opiates, may be particularly valuable.

Training to Improve Cognitive Functioning

Training forms the most fundamental core of post-injury rehabilitation. Training involves specific activities that guide changes in brain functioning based on specific learning goals. Within the training approaches, different learning goals may be defined.

Training may emphasize the learning and application of cognitive skills and/or strategies. Strategies that help to organize behavior may be helpful in improving the efficiency or effectiveness of accomplishing particular tasks. Strategies, once internalized, may be thought of as providing intrinsic "tools" available to an individual to help accomplish particular tasks. Effective application of a strategy typically results in an immediate beneficial effect; however, the long-term benefits depend on a number of factors. Factors to consider include to what extent the strategies are context-specific or transferable to other contexts, to what extent the individual can learn and remember the strategy, and to what extent the individual will be able to prospectively initiate use of the strategy in the appropriate situations. For example, it is not uncommon for an individual to be able to learn a strategy during therapy (e.g., a method for breaking problems into manageable steps), but then fail to apply this strategy when faced with a real-world problem. Such failures of transfer may be directly related to an individual's cognitive deficits.

Available literature on treatment of combat-related "mTBI" is sparse. A recent pilot study examined strategy training in combat veterans with mild cognitive dysfunction and a history of TBI [125]. Training involved a variety of compensatory internal and external cognitive strategies, including day planner usage in a structured group-based format. Following training, participants reported increased use of compensatory cognitive strategies and day planners, increased perception that these strategies were useful to them, increased life satisfaction, and decreased depressive, memory, and cognitive symptom severity. Storzbach and colleagues [126] also recently reported success with training veterans with mTBI compensatory cognitive strategies, which included a range of targets such as time management, goal setting, organization, self-monitoring, sleep hygiene, and internal and external memory strategies. Relative to veterans undergoing usual care, veterans receiving compensatory cognitive training reported fewer cognitive and memory issues and greater strategy use at 5-week follow-up. They also evidenced greater improvements on neurocognitive tests of attention, learning, and executive functions. Cooper and colleagues [127] found that therapist-directed cognitive rehabilitation either alone or combined with cognitive–behavioral psychotherapy reduced functional cognitive symptoms in military service members with mTBI compared with psychoeducation or medication management. These preliminary investigations are encouraging and suggest that cognitive training that includes compensatory strategies may confer functional and/or neurocognitive benefits to post-acute TBI patients [128].

A skills-based approach may also be taken. Though the distinctions between strategies and skills may blur, skills may generally be considered as the integrated use of particular neurologic functions or processes for the accomplishment of functional tasks. Skill training is generally considered a more gradual process, with improvements accumulating over repetitive practice. Skills may be further divided into the concepts of "neurologic skills" (based on definable neurocognitive processes which are applicable to multiple tasks or situations) or "functional skills" (procedures for accomplishing a task, such as making a sandwich). The latter may blur the borders between potentially separable cognitive processes, but this is ecologically relevant as real-life tasks typically require the integration of multiple neurologic processes.

These differing approaches may help to achieve different goals in rehabilitation. For example, it is theorized that if fundamental neural–cognitive processes are improved, then the benefits will more likely carry over to tasks and contexts outside the training. On the other hand, training on specific actions (functional tasks) may be thought of as consolidating a particular task-specific skill or procedure. As such, the behavioral improvements may be more immediately apparent as patients improve in task performance, but the improvements may be task- or context-specific. The choice of approach may depend on the nature and severity of cognitive deficits. It has been argued that functional approaches may be more effective for patients with severe deficits [129].

The utility of training that targets specific neurologic processes remains controversial, and this is an active area of research and development. Process-targeted methods have typically involved practice on tasks "isolated" from complex real-world situations. The development of training programs that target neurologic processes and result in effective and ecologically relevant gains remains an important frontier for further advancement in intervention development. Optimization of methods for higher level cognitive functions continues to be a challenge. Advances in neuroscience, informed by clinical concerns, provide a foundation for defining, targeting, and training cognitive functions. In the next section, we outline the foundations for process-targeted, neuroscience-driven interventions that address important functional goals.

Cognitive Neuroscience Foundations for Rehabilitation Training

Although a wide range and variety of deficits can result from TBI, symptoms in two general areas stand out as some of the most common and disruptive to patients—"executive control" and memory. The abilities of paying attention, holding information in mind, organizing, and developing efficient strategies for completing activities seem to be particularly vulnerable to TBI. These processes come together in the regulation and control of other, more basic neurologic processes based on goals and are often referred to as "executive control" functions [130, 131]. Although problems with memory are some of the most commonly reported complaints after TBI, the actual deficits may be quite varied. Processes important for goal-directed behavior, learning, and memory will receive special focus in this section.

Functional Impacts of Cognitive Dysfunction and the Impetus to Address Them

Processes important for goal-directed behavior, learning, and memory are fundamental for successful independent living, and deficits may directly contribute to poor outcomes. At the broadest level, poor executive control leads to disorganized behavior that affects numerous aspects of personal functioning. Executive control functions are crucial for the pursuit of educational and occupational goals [36, 132–134], with TBI resulting in an increased rate of job turnover and reduced job status [134]. However, the effects may be even more fundamental in the process of recovery from brain injury.

As empirically observed by rehabilitation clinicians, if certain cognitive functions are not intact, other attempts at rehabilitation are made much more difficult. Who, after all, are the most difficult individuals to teach? Which patients are most likely to be labeled as "not ready" for intensive rehabilitation efforts? Individuals who cannot pay attention, hold information in mind, and actively participate in learning activities may have reduced benefit from rehabilitation training efforts for other neurologic domains [21, 135–138]. As a frontier reaching beyond simply triaging patients, the remediation of these functions may be valuable for influencing learning and recovery in other neurologic domains. For example, improved goal-directed functioning may enhance an individual's ability to actively participate in attempts to rehabilitate motor functions, allowing an individual to hold learning goals in mind, selectively focus attention on learning activities, and solve problems in the numerous intervening steps between a current state and achieving a learning goal. Finally, individuals with brain injury spend a

much larger amount of time on their own than with a therapist; thus, the importance of executive control and memory functions translates to an individual's ability to self-teach skills, remember strategies, and self-adjust to residual deficits in any domain.

Foundations for Training: Neural Bases of Cognitive Functions Important After TBI

It is conceptually simple to understand how one might train motor strength by training particular muscles, but how would one prescribe training for "executive control" functions? Reviews of interventions have noted a gap between theories about subsystems of executive functions and intervention design and practice [139–141]. A better understanding of the nature of the specific underlying neural processes as well as mechanisms of learning and recovery specific to these functions may help advance treatment development [142–144].

Neurologic deficits caused by TBI are not unique to trauma per se, but certain patterns of dysfunction are more common with TBI than other causes of injury. While these patterns are partially explained by traditional neurologic localization with focal cerebral lesions, the localization approach has left many TBI sequelae poorly explained. Basic abilities, such as ambulation and speech, may be spared, and the impact of deficits may only become clear when individuals are challenged by the complexities of real life. Deficits in executive control functions are generally attributable to damage to prefrontal systems, which include not only PFC per se but also extensive interconnections with subcortical and posterior cortical structures [143]. The importance of axonal injuries in TBI highlights the need to understand brain functioning in terms of distributed but coordinated network processes [142]. "Diffuse axonal injury" without focal cortical lesions has been shown to lead to changes in executive working memory processing activity [141].

PFC is involved in multiple major networks [145]. One major network involves connections with posterior parietal cortex as well as anterior and posterior cingulate and medial temporal lobe regions [146]. Another major network involves cortical–subcortical connections between the PFC and the striatum, globus pallidus, substantia nigra, and mediodorsal nucleus of the thalamus [147]. Additional interactions with other more posterior brain regions such as sensory or motor cortex are likely important for the domain specificity of control processes [148, 149]. Deficits may also be related to damage to neuromodulatory pathways from the base of the brain to the cortex. These interactions are crucial for the modulatory control of distributed neuronal activity in order to facilitate processes that are relevant to internal goals while suppressing non-relevant processes [150–152].

How is goal-directed control implemented in neural systems? At the simplest level, neural aspects of control involve modulation of neural activity from the "top-down" based on goals, as well as coordination and monitoring of distributed neural networks in the brain. Without such control, activity would be either driven by low-level processes, such as by "stimulus-response" principles, or generally disorganized, with poorly coordinated activity that lacks guidance by a higher level goal structure. The modulation of neurologic processes from the "top-down" is accomplished by at least two important general mechanisms: *selection* (enhancement and suppression) of neural activity based on goal direction and active *maintenance* of goal-relevant neural activity for the accomplishment of tasks. The functional integration of neurons within local networks is also important. The neural representations of information appear to be coded not in single neurons, but rather in networks of neurons. For example, representations of the myriad possible visual objects, including household objects, faces, etc., have been shown to be encoded in a distributed architecture [153]. This organizational architecture allows for a much wider range of information to be encoded with a limited number of neurons. Otherwise, if a separate neuron were needed for every item or variation of information stored, the number of neurons needed would far exceed what exists in the human brain. Distributed injury, atrophy, or degeneration could disrupt neural processing even in the absence

of obvious cortical lesions. Examples of this may occur in age-related degeneration [154] and are likely to occur in TBI as well.

Thus, understanding the importance of network interactions is an important foundation for understanding the functional consequences of TBI, which might otherwise be labeled "non-focal." This also has implications for the measurement methodologies to be used to understand neural mechanisms of injury, learning, and recovery in rehabilitation studies. Examples of this frontier are discussed at the end of this chapter.

Cognitive Functions as Potential Targets of Therapy

Functions for Goal-Directed Control: Attention and Other Component Processes of "Executive Control"

Control over neurologic functions to accomplish goals may involve control over perception and information processing, motor actions, emotional functioning, as well as other aspects of behavior. One way to organize our conceptualization of control functions is to consider the components required for successful goal attainment. (For additional discussion, anatomically based schema for subdividing frontal functions [141, 155] and goal management steps have been reviewed by others [156, 157].) Deficits in any component may disrupt efficient and effective goal attainment:

- At the outset, a *goal* needs to be generated and/or selected. Whether the goal is simple or complex (e.g., make a cup of coffee vs. apply for college), inability to generate clear goals, or deficiencies in evaluating and selecting a manageable goal, will obviously result in poor goal attainment.
- This goal will then be important for guiding all subsequent processes. An *attentional set* based on the selected goal needs to be established, framing all upcoming information or actions [158–160]. Poor establishment of the appropriate set will make it more likely that the individual will be distracted or take the wrong path.
- Goal attainment activities need to be *initiated*, and this depends on motivation and an appropriate level of alertness or arousal. Apathy, depression, and low arousal (such as from fatigue) may lead to poor initiation.
- Goal attainment activities including determining the optimal *plans* to accomplish the main goal. Planning includes more in-depth analysis of the goal and breakdown of the goal into an appropriately sequenced series of subgoals (steps), including re-organization of potential actions in relation to the main goal. These processes may require interactions across a hierarchy of prefrontal networks [161].
- *Strategy* determination and related processes of planning are crucial for efficient goal attainment, especially with more complex tasks. This higher level function is relevant for learning, memory, and problem-solving. Patients with frontal injuries show impairments in strategic planning and organization of information [162, 163].
- Some goals may require more complex levels of planning, and *maintenance of the goal* during this process can be important. The planning process can be thrown off track with forgetting of the main goal or disconnection of planning from the goal (one form of "goal neglect") [164].
- Translation of the imagined cognitive sequences (plans) into action requires a step of *initiation of action* that is separable from the initiation of planning and decision-making and is another point at which an individual may stall.
- Once actions are initiated, goals and plans need to be maintained to accomplish each subgoal and the sequence of subgoals that build toward the main goal. *Goal maintenance* becomes increasingly important with goals that require multiple steps over extended periods of time, as the risk of going "off track" increases [165, 166]. This may be another form of "goal neglect" [164].
- Throughout the goal attainment process, the individual will likely be exposed to vast amounts of information (from perception or memory)—some of this will be relevant and

some non-relevant to the goal. Positive selection of goal-relevant information for deeper processing (with the complementary negative selection of non-relevant information) at the outset and at every stage of the goal attainment process will be necessary to reach the goal, or else the individual may be distracted or even overwhelmed. Selected information needs to be maintained, at the exclusion of other competing information, to accomplish each step toward the goal. The *selection and maintenance of goal-relevant information* involves processes often referred to as selective attention and working memory, functions that are integrally related [167–174].

- Similarly, a plethora of actions is possible at any moment in time, but only a selected few will be goal-relevant. *Response selection and inhibition* refers to the ability to select between competing alternatives and to inhibit inappropriate response tendencies [175, 176].
- In determining appropriate actions, multiple considerations may need to be integrated. Relational integration requires the ability to integrate multiple relationships and is crucial in problem-solving and reasoning [177, 178].
- There may be a need to transition between tasks, such as to move to the next subgoal or to deal with an interruption and yet return back to the goal-relevant path. *Direction and redirection* of attention, information processing, and actions is necessary for successfully making these transitions. Patients with frontal lesions are relatively impaired on tests that require switching between tasks or attentional sets [179].
- Once actions are taken, the results that follow may or may not be relevant to goal attainment. Comparison of results with the original goals and detection of disparities or errors is necessary for correction of the above series of processes to ultimately achieve the goal. However, neglect of the goal, deficits in awareness of errors, as well as failure to take corrective actions are major impediments to successful goal attainment.
- Independence in the above processes, and cognitive functioning in general, requires some ability to *generate* ideas and information with minimal cuing, especially for processes that require creativity and/or problem-solving. Aspects of generative ability may be impaired with brain injuries [180–182]. Overall, frontal systems appear to be broadly important for core abilities that allow a person to flexibly and adaptively solve problems across multiple contexts [183, 184].

Functions of *learning and memory* are integrally intertwined with all of the above processes of goal direction. Thus, this discussion treats these processes as part of the ensemble of functions needed for goal attainment. For example, information, strategies, and skills need to be learned and remembered so that they may be applied to problem-solving and goal attainment. Conversely, learning and memory are also dependent on many of the control processes discussed. Indeed, one of the most common subjective complaints after TBI is problems with "memory."

The underlying sources of these complaints may vary. Deficits related to declarative or episodic memory may be related to damage to medial temporal structures. The basal forebrain and long tracts that connect the forebrain to other structures are also important for memory processing. The basal forebrain, a major source of cholinergic projections throughout the brain, is particularly vulnerable to injury, and, furthermore, long projections may be vulnerable to shearing injury [185]. However, complaints of problems with "memory" do not necessarily equate to problems with these structures.

Problems with memory encoding and retrieval may also be related to attention and "frontal executive" functions that influence the selectivity and depth of information processing, as well as the ability to organize information to be encoded and strategically retrieve information to be recalled [186]. Encoding and retrieval of information from memory may be impaired in individuals with frontal system dysfunction. Important aspects of encoding and retrieval of information from memory appear to be mediated

by the role of PFC in activating, maintaining, and organizing information in working memory, as well as in re-activating and retrieving stored information [187, 188]. A common deficit seen is that a patient has difficulty on free delayed recall, but when provided with a retrieval strategy (cue), his or her performance improves. An additional set of functions is important for the "prospective" memory of upcoming events or actions [189].

Behavioral approaches to compensating for or training memory have been reviewed elsewhere (e.g., [190]). For patients with severe deficits in declarative memory related to mesial temporal injury, external aids are particularly valuable. Evidence to date argues against significant potential for remediation of such memory deficits, though this has mainly been examined in the context of hypoxic injury. However, memory problems related to deficits in controlled aspects of encoding and retrieval (related to executive control functions) may respond well to training, such as with strategies for selecting or organizing information for memory. Thus, distinguishing the underlying etiologies of memory complaints may be highly valuable in therapeutic decision-making.

Pharmacotherapy

A number of options for pharmacotherapy currently exist; however, there are relatively few data to guide the optimal choice of agent for any given individual. Pharmacotherapy is primarily empiric, but guidance might come from some definition of the treatment target (e.g., speed of processing vs. memory), theoretical considerations (e.g., likelihood of cholinergic vs. dopaminergic vs. noradrenergic dysfunction) , as well as management of other comorbidities (e.g., depression, fatigue, insomnia, anxiety, headaches). One of the important general principles, or aspirations, is that the use of these agents may increase the rate of learning and recovery.

Dopaminergic and mixed catecholamine agents may be useful for improving aspects of cognitive functioning in patients with TBI. Methylphenidate probably has the greatest amount of supportive evidence for use after TBI [50, 191]. Trials have documented improvements in aspects of attention and speed of information processing following TBI [192]. Methylphenidate may also improve learning and memory functioning after TBI by improving attention to information. Dextroamphetamine may also help to improve aspects of attention and speed of processing, but there are few data fully testing its effects in chronic TBI [193]. Bromocriptine may enhance aspects of executive functioning in patients with severe TBI [51], but again data are mixed [194]. Amantadine may improve executive function, in addition to alertness [195]. Atomoxetine has shown promise in other settings, but when tested in a relatively large randomized, controlled trial for TBI, no effects on testing and subjective measures of attention could be detected relative to a control group [196]. As a general guideline, dosing of agents that modulate catecholaminergic function should be based on individual response, noting that neuromodulatory effects tend to follow a U-shaped curve that may vary in dose-relationship for each individual.

Acetylcholine systems may be particularly important to address given the predilection for TBI to damage medial temporal structures, the basal forebrain and long tracts that connect structures important for memory processing. The cholinesterase inhibitor donepezil has been recommended to enhance aspects of memory function for patients with moderate to severe TBI in subacute and chronic periods of recovery based on trial data [50, 197–199]. Some data support the use of rivastigmine for improving memory deficits as well in patients with moderate to severe memory impairment at baseline [200, 201]. In general, these cholinesterase inhibitors appear to be safe and well-tolerated in patients with TBI. Problems with memory encoding and retrieval may also be related to frontally mediated functions, such as selectivity and depth of information processing, ability to organize information to be encoded, and ability to strategically retrieve information to be recalled. Methylphenidate, amphetamines, and

other agents that enhance attention or executive control may also improve learning and memory functioning after TBI. To what extent these medications are indicated for mTBI, such as from blasts, needs to be further tested, and additional considerations of the interaction with anxiety and PTSD need to be considered.

Maximizing synergies between pharmacotherapy and training therapies is an important frontier where strategic transitional use of medications could enhance response to behavioral therapies. This approach could contribute to a long-term goal of improving an individual's intrinsic functioning, thus allowing pharmacotherapy to be reduced over time.

Targeting Cognitive Functions: Integration of Component Processes

In sum, each component process provides a potential target for intervention. This is summarized in a schematic (Fig. 2).

Discussed as separate processes, the above may seem like a confusing and complex array of functions that are difficult to understand or target. However, an important principle is that the component processes need to be *coordinated* or *functionally integrated* in the accomplishment of any particular goal. Goals may be conceptualized as serving to functionally organize the multiple neural processes necessary for accomplishing the goal, including selecting the relevant pathways or processes (while excluding others), coordinating them at any given moment in time, and dynamically adjusting this coordination while maintaining the central goal across time to eventually accomplish the goal. Thus, not only the components but also their functional coordination may be important targets for intervention. Process-based approaches may be analogous to isolating and working out the biceps muscle, while functional approaches may be analogous to training the coordination of multiple muscles to accomplish basketball 3-point shots. A more advanced question is whether training that involves functionally integrated approaches may actually serve as an effective, more motivating way to improve underlying component processes.

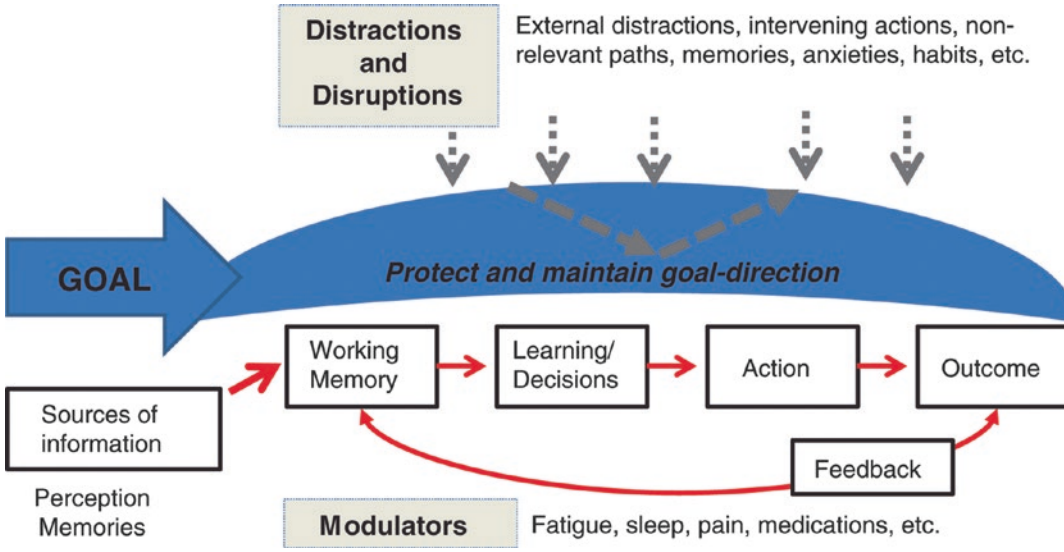

Fig. 2 Component processes in pathways to goal attainment: targets for intervention. All the main processes, *connected in red*, work together for goal attainment and are potential targets for interventions. An overarching target for strengthening involves abilities to protect and maintain goal-directed processes from distractions and disruptions, which may otherwise affect any component in the pathway. As discussed separately, other potential modulators may influence the central processes and are also potential targets for other forms of intervention

Principles for Training and Improving Functions of Goal-Directed Control

Functions that subserve goal-directed behavior are a particularly important training target for individuals with TBI. This encompasses functions that have far-reaching influence on neural processes in almost any neurologic domain, crucial to navigating the challenges of learning and adaptation after injury. Given the difficulty in understanding and designing interventions to improve goal-directed cognitive functioning, we have proposed some basic principles of training could be incorporated into interventions to target and maximize improvements in these functions [143].

Many of the methods applied in clinical rehabilitation are designed for the learning of strategies that compensate for deficits. We focus here on possible approaches for improving goal-directed control deficits, a challenging but worthwhile goal that remains at the frontiers of clinical rehabilitation. These principles may not only bolster therapies where goal-directed cognition is the primary target of therapy but may also be incorporated into cognitive, motor, speech, or other therapies in order to maximize the targeting of frontal system functions in any of these contexts. Furthermore, increasing the engagement of goal-directed control in these settings may maximize improvements across domains:

1. Training of process, not content: cognitive training tasks should challenge patients to engage "top-down" modulatory processes mediated by PFC networks.

   Tasks that require selective processing of competing information based on task relevance (selective attention), working memory (e.g., the maintenance of information over a short period of time and especially manipulation of that information), performance of dual tasks, as well as goal–subgoal management have all been shown to engage the PFC networks [143, 158, 159, 167, 202]. During the performance of these tasks, it is the processing demands, and not the specific contents of stimuli per se, that engage PFC networks. For example, PFC networks are engaged during working memory tasks regardless of the type of information (e.g., words or objects) that must be remembered [203, 204]. Thus, training needs to target specific top-down control *processes* and not *specific task content*. This contrasts with training that emphasizes repetition of task content, which promotes a shift toward automatic processing and disengagement of PFC-mediated control [205], as well as knowledge-based education approaches. Importantly, examination of the neural substrates of these functions emphasizes the engagement of *networks across multiple brain regions*, not just the PFC. This is particularly relevant to patients with "disconnection" injuries. Therapies that target control processes may be a way of promoting the "re-integration" of damaged brain into functional networks [142]. Targeting core PFC functions in process-oriented training should increase the likelihood of generalization of gains to new contexts, although this may not be sufficient without additional considerations.
2. Cognitive training should explicitly include a goal-based approach.

   The role of goal-based executive processes may be to functionally organize the multiple neural processes necessary for accomplishing the goal, including selecting the relevant pathways or processes (while excluding others), coordinating them at any given moment in time, and dynamically adjusting this coordination while maintaining the central goal across time to eventually accomplish it. In the development of a training protocol, it is important to consider the processes required for accomplishment of any specific goals during training. These processes will differ depending on the nature of the goals. For example, if the goal is to make a quick decision regarding a left vs. right button press based on an image on a computer screen in an isolated setting, then the engaged processes and the level of integration necessary will be very different than what is engaged by a more complex task, such as paying attention to one's supervisor in a noisy office in order to

accomplish an extended project. Thus, the opportunity for the greatest engagement of goal-direction processes will be provided with complex goals.

A goal-based approach will allow training of multiple goal-direction processes. Who sets the goals? *Goal generation* involves the highest levels of goal-directed control, requiring generation de novo or retrieval and appraisal of potential goals that will guide behavior. Training that involves an active role for the trainee in defining the goals and subgoals of the tasks being learned may differ in effect from when goals are "assigned." Coordination of the many steps required for goal attainment may critically rely on the protection and maintenance of the goal. Thus, goals which require greater lengths of time and multiple tasks to accomplish will provide greater challenge to *maintenance* of goal information. What is the *personal relevance* of the goals to the individual? It is important for several reasons that the goals of training are of significance to the patient: this will increase motivation, encourage application of skills to ("real-life") goals that are often more complex than "artificial" goals, and allow for increased practice of goal processing in daily life. There is also the potential for increased positive feedback from accomplishment of goals that are important to the trainee. Incorporation of some or all of these features would significantly affect the nature of the intervention and likely benefits.

3. Cognitive training tasks should progressively challenge the patient.

The importance of progressive increases in challenge difficulty and complexity level is underscored by the ability of the brain to adapt to tasks. Even tasks that engage goal-directed control processes may become less challenging with practice and, thus, less effective at encouraging learning in the targeted domain. As a patient's level of function improves for a specific process, tasks may need to be adjusted such that demands for that process are increased. This is more specific than simply increasing the general "difficulty" of the task, as parameters that are adjusted should quantitatively vary the level of engagement of specific processes, such as working memory, multitasking [206], updating [207], or interference control [208]. Extensive studies on the effects of practice of well-known cognitive control tasks have documented context-specific improvements [209, 210]. Thus, simply practicing isolated, purportedly process-targeted tasks may not be sufficient to improve functioning in a significant way, even if the trainee is challenged progressively.

4. Training should explicitly address pathways for the transfer and generalization of training effects to new and real-world contexts.

A major gauge of the success of any training-based therapy is the extent to which benefits actually extend beyond the training tasks and context. As mentioned above, if functions of the core PFC networks for goal-directed control are effectively improved, then generalization of benefits should be more likely. How would this be accomplished? There are two complementary principles of use here: (1) strengthen the underlying ability and develop automaticity in the use of the ability and (2) maximize the likelihood of goal-relevant application of the skill when and where needed.

In order to effectively target and strengthen core PFC functions, and not simply context-specific abilities, it is arguably important to train the target processes in multiple modalities and multiple settings. PFC is multimodal association cortex, and PFC networks serve to integrate information from multiple modalities [148, 204, 211, 212]. Training across *multiple modalities* may maximize engagement of core PFC networks, leading to improved functioning across contexts.

Linking skill use to a goal-based framework can maximize the likelihood of beneficial skill use. The above simplified process-oriented view of PFC involvement in goal-directed control raises a question regarding the importance of the *context(s)* in which these functions are engaged. Any training context carries with it important cues and inherent structure, which may provide scaffolding for

an injured individual. Most deficits in goal-directed control are only apparent in contexts that lack strong external cues for action, requiring hierarchical organization that allows top-down goal-directed signals to out-compete bottom-up signals encouraging engagement with the environment [164, 183]. Thus, the opportunity for the greatest engagement of goal-direction processes will be provided in *unstructured* settings. Strengthening of an internal goal-based framework is vital to engaging goal-directed control abilities in these settings.

5. Meta-cognitive strategy training may provide a form of goal-directed control function remediation.

   Meta-cognitive strategies are proposed to play an important role in achieving generalizable improvements in goal-directed functioning. One hallmark of prefrontal network dysfunction is difficulty in structuring cognition and behavior by employing strategies to efficiently and effectively accomplish goals. Training to strengthen goal definition and goal awareness can help in activating goal-directed control when and where relevant to accomplishing a goal.

   Increasing clinical evidence supports the proposition that training-based therapies targeting problem-solving, involving the use of meta-cognitive strategies, may improve functioning in individuals with brain injury [139, 140, 213]. Several interventions have been developed and implemented with such an approach [157, 214–219]. For example, in goal management training [156], patients are trained to clearly define a goal, learn the steps required to achieve it, and then regularly check their progress. Engagement of PFC appears to play an important role in the successful application of strategies [220, 221]. Thus, meta-cognitive strategy training may enhance PFC-mediated control processes, rather than simply being compensatory. The neural mechanisms underlying successful improvement with meta-cognitive strategy training will be worth further investigation.

6. Training of goal-directed control of brain states.

   All cognition and behavior occur from the foundation of an underlying brain state. The effectiveness and efficiency of functioning depend on the regulation of these states as appropriate to a current goal. This leads to perhaps the most fundamental of all the training principles. Goal-directed control may be improved via improved regulation of brain states. At a neural level, modulation of brain states alters signal and noise properties of information processing systems in the brain that support abilities such as goal-directed control functions [222–224]. Thus, training that improves regulation of brain states may also improve cognitive function following brain injury. A full understanding of the regulation of brain states that is translatable to treatment considerations still needs to be developed; however, certain aspects of state regulation are understood to be important for cognitive functioning.

   It is clear that brain states established by alertness and arousal, attentional sets, emotional states, and motivation can affect cognitive functioning. For example, a state of hyper-arousal may lead to rapid shifts of attention (distractibility), while low arousal may lead to poor activation and maintenance of attention. Patients with TBI–PTSD may show severe hyper-arousal, while patients with more severe TBI may exhibit marked deficits in alertness [63, 64, 66]. Interventions that improve the regulation of arousal state may improve goal-directed functioning. External cues may help [48, 49, 225], but training to improve self-regulation, from mindfulness exercises to more recent developments with computer-assisted techniques, may also be helpful [226, 227]. Mindfulness-based training approaches may train regulation of arousal state, reduce the load of non-relevant cognitive or emotional processing on limited neuro-cognitive resources, and improve an individual's ability to redirect attention to goal-relevant processes [228–231]. A recent study illustrated that a modified

MBSR training program, Mindfulness-Based Mind Fitness Training, may help healthy military personnel preparing for deployment to regulate their emotions [232]. It is often presumed that individuals with goal-directed control function deficits due to brain injuries would not be good candidates for such training, given difficulty with attention regulation. We have found, however, that cognitive training that incorporates principles of mindfulness can improve attention, working memory, and goal-directed functioning for individuals with brain injury [231].

It is worth noting that improvements in state regulation may improve implicitly during any training intervention. For example, it is likely that trainees develop self-regulatory skills during intensive training when tasks are challenging (cognitively or physically), requiring the ability to regulate one's cognitive and emotional states [233]. Thus, even tasks that are described as task-based (e.g., computer games) may result in improvements in functioning that are due to improvements in state regulation and/or an enhanced capacity to learn. This has more recently been recognized in basic studies of the effects of video game training (e.g., [234])

7. Interactions of emotion and cognition.

Special consideration needs to be made for the importance of emotion regulation for optimal cognitive functioning. Poor emotional control can significantly affect cognition and goal attainment. Emotional and cognitive control are directly tied together in that the underlying neural systems interact significantly in achieving self-regulatory control necessary for goal-directed behavior.

Dysregulation of emotion can occur at multiple levels. An individual experiencing feelings of anxiety, irritability, and/or distress will be less able to effectively complete tasks that require overcoming challenges and solving problems, especially unexpected ones. Even further, he or she may negatively "overreact" to challenging situations, and the emotional reaction may impede the clear cognition needed for effective goal attainment. It is also likely that reduced cognitive control would contribute to poorer emotional control. Individuals with TBI, with reduced self-regulatory control, may have more difficulty in managing and altering negative and/or traumatic associations and the "triggered" emotions. For example, an inability to filter out information and demands that are not directly related to a current goal (additional "cognitive noise") may lead to increased feelings of being overwhelmed. Indeed, given the known limitations of neural processing resources, it seems logical that an increase in "load," whether from cognitive or emotional sources, would lead to less efficient overall functioning. Interventions that improve attentional self-regulation may also improve emotional self-regulation and vice versa.

Thus, in order to improve an individual's ability to learn, change, and adapt in the process of goal attainment, it will often be necessary to address both cognitive and emotional self-regulation. These issues are discussed in more detail in the next section, with a focus on the combination of TBI and PTSD, perhaps the "hallmark" syndrome of recent combat activities.

Cognition, Emotion, and Combined TBI–PTSD: Frontiers for Treatment

Interactions of TBI–PTSD

Either TBI or PTSD alone may alter cognitive, emotional, and behavioral functioning. The co-occurrence of TBI and PTSD raises the question of how the two entities interact, and whether the combination of physical and experiential trauma results in consequences not simply explained by additive effects of TBI or PTSD alone.

PTSD and mTBI may have independent and additive roles [235], but may also interact at multiple levels, including at the genesis of injury, the maintenance of symptoms, various aspects of cognitive–emotional functioning, and at the level of neural mechanisms. Features of each may interact to worsen functioning and/or

make treatment more difficult. Approaching TBI–PTSD will require a multifactorial approach that addresses multiple, interacting layers of functioning. Furthermore, potential special features of the combination may need to be addressed. Defining certain core targets of intervention, such as processes of self-regulatory control important for both TBI and PTSD, may provide a gateway to enhance the success of other aspects of therapy. Special considerations are discussed in more depth in each section below.

Interactions Between Cognitive and Emotional Functioning with TBI–PTSD

Although TBI can result in dysfunction in almost any neurologic domain, the most common and persistent deficits tend to be in the *control* of cognitive–emotional functions. Indeed, injured individuals may be able to engage basic functions, but the disrupted regulation of these functions leads to variability, lability, and inconsistency. As a classic example, some individuals with TBI display emotional lability, in one instant cooperative and friendly, in the next instant irritable and angry. This may be due to cognitive factors, such as misinterpreting or overreacting to environmental stimuli, as well as issues in the control of emotions or behavioral expression. This characterization overlaps greatly with PTSD. Effective regulation of emotion is crucial for optimal cognitive functioning. Dysfunction in emotional control, leading to frustration, irritability, anger, or even apathy, may significantly alter cognitive performance.

In another example, individuals may commonly complain of reduced ability to pay attention and hold information in mind, affecting many aspects of life functioning. However, attentional processes may be disrupted by "noise" from both "external" and "internal" sources. For example, it may be difficult to concentrate on a single conversation when other conversations are being heard in a crowded room, or it may be difficult to focus on a lecture during class when emotion-laden thoughts are also distracting from processing that goal-relevant stream of information. Should these symptoms be attributed to TBI or PTSD? Or is that the wrong question?

The Occurrence of PTSD May Add to the Cognitive Dysfunction Associated with TBI

The addition of PTSD to TBI may contribute to cognitive difficulties. The most common cognitive deficits associated with PTSD involve attention, executive functions, and memory [236]. Attention and executive function deficits commonly found in PTSD include working memory difficulties [237, 238], problems in sustaining attention over time [239], response inhibition [240, 241], and impaired ability to gate, monitor, and regulate the flow of incoming information and environmental stimuli [241].

A number of studies have documented impairment in learning and remembering new information in PTSD patients. With respect to learning new information, impairments in PTSD have been noted on both verbal and visual memory tasks but are more pronounced on verbal memory tasks [242]. PTSD-related deficits have been observed at different stages of memory processing, including the initial registration of new information and, somewhat less commonly, in retaining the newly learned information over time [236, 243].

Could TBI Contribute to the Development and Sustainment of PTSD Symptoms?

There are clearly commonalities in terms of the external events that generate physical and experiential trauma. Could TBI contribute to the development and sustainment of PTSD symptoms? The occurrence of TBI could actually increase the risk of development of PTSD. Repeated exposure to experiences involving fear, horror, or helplessness in situations of threat to life or well-being is common in combat.

In the post-deployment health assessment and re-assessment of 88,000 soldiers, 53% witnessed someone wounded or killed, 49% felt in danger of being killed, and up to 42% required mental health treatment, with PTSD reported in up to 25% [244]. There is an increased risk of PTSD with personal physical injury. In particular, there is an increased rate of PTSD for those with TBI (RR 1.8) [245]. In examining the incidence of PTSD, rates increase in relationship to the occurrence of mTBI, with increased incidence of PTSD along the gradient of no TBI to altered mental status to LOC [39]. All of these numbers argue that some aspect of TBI contributes to the development or sustainment of PTSD symptoms. From the initial instant of injury mechanism, physical and experiential injuries are intertwined. However, there are likely additional interactions that contribute to symptom maintenance across time.

Cognitive Dysfunction May Impede Treatment for Emotional Problems, and Emotional Dysregulation May Impede Treatment of Cognitive Dysfunction

Severe emotional control dysfunction, including anxiety, hyper-vigilance, and avoidance, may become significant barriers to treatment of cognitive issues. On the other hand, cognitive deficits, especially those affecting aspects of attention, learning, and memory, may become barriers to effective treatment of emotional issues. Existing interventions designed for TBI rehabilitation or PTSD alone may need to be modified in order to maximize effectiveness. The modifications may require crossing the boundaries between traditional disciplines, creating a significant challenge in care systems designed to address single diagnoses.

Modifications to Existing Treatments

In current practice, most interventions are directed toward a diagnosis of PTSD or TBI, but not both. Treating PTSD, in the context of TBI, may differ from treating PTSD alone. For individuals in the chronic phase of the disorder, the PTSD treatments with the strongest evidence are cognitive–behavioral psychotherapies [246] such as cognitive processing therapy as well as prolonged exposure [247, 248]. Preliminary data also suggest that these therapies will be helpful for Operational Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans. A small ongoing trial of prolonged exposure among OEF/OIF veterans has shown a 50% reduction in PTSD symptoms following treatment [249]. There is some evidence supporting the effectiveness of CBT for the treatment of acute stress disorder following mTBI and CBT combined with neurorehabilitation for targeting general anxiety symptomatology in people with mild-to-moderate TBI [250]. One type of trauma-focused therapy that has received widespread empirical support is cognitive processing therapy (CPT). As in other CBT variants, CPT primarily focuses on challenging maladaptive beliefs as a means of improving well-being. CPT specifically focuses on developing strategies for evaluating and changing unhelpful thoughts about oneself and the larger environment and/or world that develop in response to a traumatic event and which contribute to dysfunction and poor adaptation. A recent retrospective analysis by Davis and coauthors of CPT for 136 veterans with PTSD showed no difference in treatment completion rates between veterans with or without a history of mTBI [251].

Modification of these approaches for individuals with cognitive dysfunction remains an important frontier for intervention development. Current experience suggests that PTSD in individuals who also sustain a TBI may be more complicated, and the chronicity of symptoms may be extended. Patients with TBI–PTSD may respond differently to standard treatments compared to those with only TBI or PTSD. Cognitive limitations may make it necessary to modify cognitive–behavioral therapies, and emotion regulation and impulse control problems may complicate the use of exposure techniques. Physical pain, which frequently occurs after TBI, may

limit the extent to which patients can engage in PTSD treatments that involve in-person exposure to anxiety-producing situations [252, 253]. Conversely, the emotional dysregulation, avoidance, and potential for triggering may impede engagement in cognitive rehabilitation therapies. Reduction of PTSD and management of severe TBI may be facilitated by teaching patients more adaptive coping strategies [254].

Interventions for TBI–PTSD

Recognizing complexities with regard to TBI diagnosis and attribution of symptoms, a recent VA directive stated the following: "The assessment of an individual with persistent concussion/mTBI-related symptoms should be directed to the *specific nature of the symptoms regardless of their etiology*. The *management* of an individual who has sustained a documented concussion/mTBI and has *persistent* cognitive and behavioral symptoms after 1 month should not differ *based on the specific underlying etiology of their symptoms* (i.e., concussion vs. pain, concussion vs. stress disorder)."

Combined approaches for co-treating the variety of emotional/behavioral and cognitive sequelae may need to involve mental health/PTSD specialists and TBI rehabilitation specialists [235]. Therapeutic formulations may also need to address associated issues with substance use disorders, pain, and the other issues discussed in this chapter.

Vanderploeg and coauthors discuss the need to intervene early after military post-deployment with social and emotional adjustment interventions, including the development of mindfulness-based relaxation and stress management skills, improved sleep hygiene, and education regarding substance use/abuse and alternative coping supports [235]. They further suggest that early symptom-based adjustment and stress management interventions may minimize the development or prolongation of PTSD and additionally may serve to reduce residual symptoms associated with TBI. Current findings also suggest that PTSD treatment likely should be prioritized after combat or other types of injury, regardless of TBI status, to decrease symptom complaints and enhance outcomes. Similarly, in a recent study, 40 VA rehabilitation providers interviewed [255] indicated that patients with PTSD and history of mTBI require more repetition, attention, and time to complete assignments related to their PTSD treatment.

In a recent pilot study by Cole and coauthors, nine veterans with PTSD and mTBI history participated in an 8-week mindfulness group class and reported high levels of satisfaction with the intervention. PTSD symptoms measured by the PTSD Checklist-Military version (PCL-M) were significantly improved after treatment, and gains were maintained at the 3-month follow-up [256]. Janak and coauthors conducted a multidisciplinary treatment program (which included cognitive rehabilitation, behavioral health interventions, occupational therapy, vestibular rehabilitation, and medical management) in a group of 257 active duty service members with persistent post-concussive symptoms. Participants had a history of mTBI (median 5 months post-injury), and at baseline, 34% met criteria for PTSD. After treatment, both post-concussive symptoms (measured by the Neurobehavioral Symptom Inventory, NSI) and PTSD symptoms (measured by the PCL-M) declined. Of note is that the subset of participants with PTSD diagnoses had a higher number of post-concussive symptoms both before and after treatment, as well as smaller treatment effect [257].

Targeting Core Self-Regulatory Control Functions Involved in TBI–PTSD

These considerations argue strongly that treatments that effectively improve cognitive and emotional self-regulatory functions may be particularly valuable in treating the combined neurotrauma syndrome. The issues from TBI–PTSD include disruption of core cognitive and emotional regulation mechanisms that are essential for goal-directed functioning in life. Interventions that strengthen the goal-directed

control functions, such as the selection of relevant information along with inhibition of distracting information, may be particularly helpful. Dorsolateral PFC and ventromedial PFC interact in the regulation of emotions, with modulation of amygdala [258]. These interacting circuits are likely to be important for cognitive and emotional self-regulation training such as mindfulness-based attention regulation. This forms an important foundation for further development of interventions for TBI–PTSD.

Neural Bases of TBI–PTSD and Frontiers in Intervention Development

Treating individuals with TBI–PTSD symptomatically, regardless of diagnosis, is an important initial approach. However, it is possible that intervention approaches may be refined as more is learned about the underlying biology of the disorders. Consideration of potential interrelationships between traumatic and experiential injury at neural levels generates important hypotheses for guiding research and intervention development. Direct interactions may be understood based on structural neuroanatomy, functional neural network circuitry, and neuropharmacology. Neurologic abnormalities associated with TBI may complicate abnormalities associated with PTSD. Limbic structures, including the amygdala, are thought to be integral to emotions (e.g., anxiety) involved in the fear response. As a "modulator" of the limbic system, the medial PFC is thought to play a significant inhibitory role, allowing higher-order cognitive functions to moderate less volitional limbic-based fear responses. Because TBI may involve damage to prefrontal circuits, the additional loss of inhibitory control of the limbic system related to the TBI may play a role in exacerbating and maintaining PTSD symptoms.

Investigations that focus on neural mechanisms of learning and plasticity in particular will be valuable for better understanding the pathogenesis of symptoms and dysfunction as well as providing foundations for treatment approaches. Neural level considerations suggest that certain treatment approaches used for TBI or PTSD may need to be modified in order to maximize beneficial effects and reduce potential for unexpected harm in individuals with the combined syndrome. This applies to pharmacologic and other biological approaches, as well as behavioral approaches.

On a broader level, all of the above interactions argue for a reconsideration of a combined combat neurotrauma syndrome as an entity distinct from TBI or PTSD, with features that are not simply the addition of the two. Definition of this syndrome has implications for guiding future research, defining new research questions as well as requiring new approaches and methodologies. Regardless of whether we can define a definitive syndrome and its etiology, it is clear that the combinations of symptoms that veterans experience after combat do need to be addressed with available tools immediately. Addressing these symptoms will require a multifactorial approach that takes into account contributory environmental, personal, social, emotional, and cognitive factors as well as changes in underlying neural systems. In particular, a much greater emphasis on cognitive, emotional, and behavioral self-regulation may be needed, even in individuals with so-called "mild" TBI.

Tested Theory-Driven Cognitive Interventions for Attention, Working Memory, and Other Control Processes

A variety of innovations have been developed for targeting aspects of cognitive functioning. Individualization is a key tenet for optimizing rehabilitation. Thus, each therapist may provide a different intervention for each patient, and systematically studying such interventions is challenging. A small number of structured intervention protocols have been directly studied. Increasing evidence supports the proposition that training-based therapies have utility for rehabilitation in the chronic phase of TBI, including training for attention, working memory, problem-solving, and other strategic aspects of goal management.

Even within the domain of attention, there may be many varieties of approaches to training. A selected handful of theory-driven interventions are highlighted here. A new paradigmatic example is attention process training (APT), originally formulated by Sohlberg and Mateer [259, 260]. Versions of APT train a hierarchy of attention processes using guided exercises. This method, along with other clinically based approaches, has been reviewed in multiple reviews and meta-analyses [139–141, 261, 262], and there is significant evidence to support their use for patients with brain injury. This and other approaches that target specific processes, including a number using computer-based tasks, have been demonstrated to improve functioning on targeted measures. However, the transfer and generalization of gains from task practice have turned out to be an important barrier [144]. This raises important questions regarding the nature of transfer beyond practiced tasks, and the development of approaches to enhance generalization remains an important goal.

Some recent approaches have shown promise in not only improving the targeted processes but also showing transfer of benefits to other tasks that were not included in training. In a series of studies utilizing computer-based practice of tasks that progressively engage spatial working memory, Klingberg and colleagues have shown improvements in working memory functioning as well as transfer to higher level cognitive functions that presumably rely on working memory [263, 264]. In healthy subjects, improvements correlated with increases in activation in PFC and parietal regions, as well as changes in dopamine receptor binding [265, 266]. Other recent studies testing computer-based tasks with healthy individuals have generated excitement by demonstrating improvements in aspects of goal-directed control and even general fluid intelligence [206–208, 267]. To what extent process-targeted, computer-based approaches may be helpful for individuals with brain injury, with improvements that generalize to real-world functioning, will be worth further investigation.

Approaches that train the use of meta-cognitive strategies have demonstrated utility for individuals with brain injury. Noting that many individuals with brain injury have difficulties with specific aspects of goal management, including making absent-minded slips, going off track, and having difficulty completing multi-step tasks, goal management training emphasizes the cessation of ongoing activity and a meta-cognitive strategy for breaking down goals into manageable substeps. This approach attempts to ameliorate deficits related to goal neglect, and studies testing training protocols have shown that learning of these strategies may improve goal management for individuals with brain injury as well as healthy older adults [156, 268].

Another intervention that combines attention and problem-solving as targets of therapy in a group-based training protocol was recently described by Evans [269, 270]. Initial group sessions address attentional difficulties, and later sessions introduce and practice the use of problem-solving strategies. Participants are encouraged to adopt a systematic approach to solving problems and to manage and monitor goal achievement through periodic mental checking. In a study by Miotto and coauthors [271], participants with chronic frontal lesions showed improvement on a measure of functional performance with multiple tasks and on caregiver ratings of executive functioning, although not on neuropsychological tests, after the implementation of training relative to control conditions.

We are all constantly faced with sources of information that either contain too much information or are ambiguous with respect to one's goals. The ability to synthesize core meaning from incoming information (i.e., "get the gist") is important for goal-directed behavior in everyday life and relies on the integration of a number of cognitive processes. Chapman and colleagues have developed protocols to train gist-based strategic reasoning, guiding individuals through steps that engage attention (repeating and filtering the information), working memory (integration of information), and higher level elaborative reasoning (expanding, extracting). Training has been shown to improve the ability to extract gist, as well as other aspects of learning and reasoning, for both children and adults with brain injury

[272]. Performance on tests of attention and working memory also improved. This raises the interesting possibility that training in higher level integrative abilities may improve more basic functions.

Targeting the Gateways to Goal Achievement

The regulation of information processing in the brain deserves special emphasis. Selective processing of goal-relevant information, a central component of executive control, is a crucial gateway that filters what information gains access to more in-depth processing [273–277]. The integrity of information processing, whether from perception or through other steps to action, requires mechanisms of selection, maintenance, and protection from disruption during working memory, learning, decision-making, and/or problem-solving. The protection of information processing from distractions anywhere along this pathway is crucial to efficient and effective goal attainment, especially when extended time or multiple steps are required.

The general principles proposed earlier in this chapter for optimally training control functions would ideally be applied with this specific "selection" gateway as a target. In one example of a rehabilitation neuroscience study, our particular interest was in examining neural–behavioral changes with an intervention that targets goal-oriented attention regulation [231]. Participants with chronic brain injury and executive dysfunction completed a training intervention for goal-oriented attentional self-regulation (GOALS) that takes into account the links connecting attention, working memory, and goal-based direction of behavior in daily life. In contrast to training via practice on isolated tasks, this training protocol involved application of attention regulation skills and strategies to participant-defined goals in real-life, ecologically valid settings.

Two conceptual lines converged to delineate target processes for intervention. First, pathways from perception to action require mechanisms for the selection of information for in-depth processing, as well as the maintenance and protection of this information from disruption during working memory and subsequent learning, decision-making, and/or problem-solving. Second, many patients with brain injuries show an overall "life disorganization," with poor ability to manage and attain goals, even when they may be able to describe their intentions at the outset. Duncan and others have described this phenomenon as "goal neglect" [164, 183]. We reasoned that selective maintenance of goal-related information is important for guiding sequences of steps (subgoals) required to accomplish the goal. Therefore, intervening on these processes may help to ameliorate symptoms of goal neglect. The experimental training protocol was based on training interventions that have been applied to patients with brain injury as well as other populations [156, 157, 214, 216, 219, 268], with special emphasis on mindfulness-based attention regulation strategies applied to daily life situations and complex, project-based functional tasks. An overarching hypothesis was that training that improves goal-directed control over neural processing would benefit all subsequent stages of goal-based processing, helping by making damaged, poorly integrated collections of neurons into more efficient, better integrated functional networks for the performance of relevant tasks and, ultimately, goal attainment in real-life contexts.

It may be argued that the ecologically valid measurement of executive control functioning requires observation and quantification of performance with real-life, functional tasks in a low-structure environment. We, therefore, assessed training-related changes in participant functioning on measures of performance in "real-life" low-structure settings. Following training, participants showed improvements in accomplishing tasks, confirming generalization of training effects to complex, real-life settings. In testing whether functional improvements might be related to improvements in the targeted cognitive functions, we also assessed domain-specific changes utilizing neuropsychological testing. Participants who completed a course of GOALS training improved on neuropsychological measures of complex

attention and executive functions, including working memory, mental flexibility, inhibition, and sustained attention:

- A recent randomized control study of 33 veterans with a history of chronic mild to severe TBI and executive dysfunction [278] indicates similar results to the initial predominantly civilian study [231] described above, showing improvements after GOALS, but not after control educational intervention (EDU), on a neuropsychological composite measures of attention and executive function ($p < 0.001$) and working memory ($p < 0.02$) [279, 280]. Participants also improved after GOALS, but not after control EDU intervention, on complex "real-life tasks" performance—Goal Processing Scale (GPS [280, 281] (GPS Overall Performance $p < 0.01$ and Sequencing and Switching of Attention subdomain $p < 0.5$). Similarly, after GOALS, but not after matched control EDU intervention, participants indicated improvement on self-report measures of emotional regulation and functioning, including Profile of Mood States (POMS) Confusion at $p < 0.02$).
- These results suggest that improving cognitive control (attentional self-regulation in particular) may also improve functioning in other domains, including emotional regulation and complex daily tasks, and are supported by preliminary findings from a recently completed randomized control study with 40 veterans with current diagnosis of PTSD and history of chronic mTBI [278, 279]. Preliminary results of this study indicate that post GOALS, but not control EDU training, participants significantly improved from baseline on overall neuropsychological attention and executive function composite score ($p < 0.001$) and following subdomain scores: working memory ($p < 0.05$), sustained attention ($p < 0.001$), and inhibition ($p < 0.001$). Post-GOALS participants also improved on complex functional Goal Processing Scale Learning and Memory subdomain ($p < 0.05$). Participants also reported significant improvement in daily functioning on MPAI Ability Scale ($p < 0.05$), and on emotional regulation self-report measures: PTSD symptoms on PCL-M Total Score, and Re-Experiencing subscore ($p < 0.05$) and on POMS Overall Mood Disturbance and Depression ($p < 0.05$).

Long-term follow-up is particularly helpful to determine what aspects of an intervention have enduring benefits. In a follow-up conducted 6 months to 2 years post-training, 94% of participants with chronic ABI indicated continuing use of at least one trained strategy in their daily life [282]. Similarly, in a recently completed study, 21 out of 23 veterans with a history of TBI reported retaining and incorporating some of the trained strategies in their lives 6 months to 2 years following completion of GOALS training [283]. Importantly twice as many (10 out of 23) reported returning to competitive employment (compared to 5 *out of 23 prior to training*). Preliminary results from 20 veterans who also completed in-person behavioral assessments indicate that they have maintained significant improvements up to 2 years post-GOALS training relative to their pre-training performance on neuropsychological measures (attention and executive function, auditory working memory, and mental flexibility), complex functional task performance (GPS Overall Performance, Planning, Self-Monitoring, and Learning/Memory), and self-report measures of emotional regulation (POMS Total Mood Disturbance, Depression, Tension and Confusion; Beck Depression Inventory). These findings suggest that training self-regulatory cognitive and emotional control strategies applied to personally relevant situations and goals may provide meaningful and lasting improvements in cognitive, emotional, and occupational functioning and may have directly relevant applications toward helping veterans with history of TBI return to work and/or school.

Understanding the neural bases of cognition, including the mechanisms by which improvements occur, may provide guidance for the development of treatments to enhance functioning [139–143]. Intervening via rehabilitation provides an opportunity to probe such mechanisms. Functional neuroimaging studies examining

changes associated with various forms of training in neurologically intact individuals have shown different patterns of results, primarily in terms of increases or decreases in regional brain activation, and the significance of these results remains unclear [284–286]. It is also unclear from functional neuroimaging studies of patients with acquired brain injuries as to what neural changes support improved recovery of cognitive function [287–290]. Information regarding neural mechanisms of improvement in executive control functions is particularly sparse. Even the extent to which the neural systems that underlie executive control are plastic, if at all, has remained an open question. Only a handful of fMRI studies to date have examined cognitive rehabilitation following brain injury [291, 292], and even fewer have examined the effects of rehabilitation interventions on executive control functions [293]. We attempted to identify neural mechanisms that underlie improvements in attention and executive control with the above described rehabilitation training.

We hypothesized that training in attention regulation improves cognitive performance by enhancing goal-based modulatory control of neural processing. fMRI methods adapted for testing the effects of intervention for patients with varied injury pathology were used to index modulatory control of neural processing [294]. Another important paradigm shift is supported by measurements that "read the *information*" coded in brain networks, rather than simply quantifying activity levels. Information is represented in the brain through the coordinated activity of distributed networks. Methods for decoding neural information representations may provide valuable tools for gauging the functional integration of these networks, particularly important in individuals who have suffered brain injury and potentially a "disintegration" of brain networks. We hypothesized that attention regulation training would lead to changes in tuning of neural representations, such that the balance of representation would favor goal-relevant information. Our findings with training were consistent with this prediction. Modulation of neural processing in extrastriate cortex was significantly enhanced by attention regulation training.

As discussed above, the lateral PFC has been strongly implicated as a source of attentional control signals that could bias neural processing in extrastriate cortex [151, 295, 296]. The pattern of findings within lateral PFC showed that changes in function depended on the baseline state of any given individual. One particularly important but challenging question for further investigation is to understand the individual variability in mechanisms by which different individuals may achieve improvement in functioning after brain injury.

Harnessing Technology to Enhance Neurocognitive Skills Training

A central goal of any program of cognitive rehabilitation is to promote functional improvements in the everyday lives of patients with brain injury, particularly related to navigating the complexities and ambiguities that characterize most low-structured settings in the real world. We argue that for rehabilitation to effectively achieve this functional goal, training must include a range of activities that allow for generalizable neurocognitive skills to be sufficiently learned, practiced, and developed [231, 297, 298]. It is particularly important that these experiences include practice with managing the types of cognitive–emotional challenges that commonly interfere with goal-directed functioning for persons with brain injury, such as being overwhelmed by too much information, tolerating frustrations, managing distractions, and coordinating and following through with multi-step plans, especially when steps are distributed over time and space.

In our previous work [231, 294], we emphasized training skill use directly within the context of participants' individually defined goals as one especially valued training experience. An aspiration of this approach is to facilitate supported skill practice (via individualized coaching) in naturalistic settings and on the types of everyday activities that many with brain injury report experiencing difficulty performing. However, there

are both theoretical and practical limitations to the degree of "hands-on" coaching and guidance practitioners can provide to their patients in the community. Outside of the observable clinical setting, it is often unclear to what extent patients follow through with agreed upon treatment plans; opportunities to practice skill use may be missed altogether, or skills may be implemented inadequately (or even incorrectly) in identified situations. A clinician's primary source of information in such instances is patient self-report, yet these accounts may be incomplete or inaccurate due to common sequelae of brain injury, such as poor memory, limited self-awareness, or lack of insight [183, 299]. This can result in missed opportunities to guide and influence ongoing skill development. Incorporating more active learning opportunities directly into clinical rehabilitation, including those that readily allow for skills to be modeled and directly observed so coaching and feedback can be provided, may enhance the overall effectiveness and long-term benefit of neurocognitive skills training.

In addition, there are many intermediate steps between initial skill learning and the ultimate successful application of skills in community settings that need to be explicitly addressed for clinical rehabilitation to best promote robust functional gains [300]. First, and as noted previously, skills training would ideally involve tasks of increasing challenge; many patients with brain injury would benefit from achieving a degree of skill mastery on relatively easier tasks before progressing to more complex ones. Once these more complex tasks have been introduced, patients may then benefit from practicing skills in additional contexts involving higher-order challenges, such as with managing distractions and disruptions to primary task activities. It is difficult if not impossible to achieve this degree of environmental control in most real-world settings. Second, it is imperative during early stages of skill learning that the consequences of skill practice are benign. Failures with skill use are an expected and important component of the learning process [301]. If skills are prematurely applied in real-world settings to ill effect, it may undermine the perceived utility of skill use as well as discourage skill experimentation–factors known to play a critical role with promoting skill use over the long-term [302, 303]. Thus, patients may benefit from training activities that allow for skills to be practiced but which do not carry overly harmful inherent risk.

To address the needs identified above, we recently developed a training system to better support the stepwise learning of self-regulation skills for patients with brain injury [300, 304, 305]. This approach integrates skill instruction, interactive coaching, and intensive skill practice across multiple contexts and settings, including in digital game-based scenarios. Contrary to many training programs that utilize gaming technologies (see [306] for a comprehensive review), we integrated digital scenarios directly into training for the explicit purpose of providing a platform where trained self-regulation skills can be practiced and developed. Thus, the overarching purpose of gameplay is to provide varied and multiple contexts to practice self-regulation skills. The lack of explicit and generalizable skills training involved with many computerized brain training programs that adopt drill-and-practice methodologies may be one reason why that approach has limited evidence of transfer [307–310].

We designed digital scenarios in consultation with individuals with brain injury to reflect difficulties that they commonly experience, such as holding information in working memory, managing distractions, multitasking, and making goal-based decisions. Cognitive challenges within game scenarios were parameterized across multiple indices and are continually adjusted based upon performance to engage patients at the upper bound of their demonstrated capacity. One gameplay revolves around the establishment of a food truck business, and trainees are tasked with fulfilling orders following a brief on-screen presentation. While completing this central task, trainees are exposed to distractions in the form of passersby who make varying requests requiring immediate action. These occur at different phases of goal pursuit (e.g., encoding vs. action) and differ in their intensity. Gameplay increases in complexity over the course of training to involve

different scenarios requiring goal prioritization, multitasking, and self-monitoring.

Gameplay is incorporated into an overall training framework in order to facilitate skill learning and skill transfer. Self-regulation skills taught during training sessions are first modeled by trainers in the context of gameplay before trainees practice and experiment with skill use on their own. Objective feedback is provided to trainees both immediately during gameplay as well as in summary form during each training session. This helps to establish clear links between gameplay, skill use, and game performance. Trainers work closely with patients to help identify game junctures where skill use might be helpful, establish plans for utilizing skills in those instances, and develop and refine their application. Gameplay experiences are further utilized to facilitate discussions on how trained skills can be applied in trainees' individual lives. For instance, a trainee may be asked to articulate the nature of challenges within the game world and then will be guided through similar discussions using hypothetical and real-world examples. Game experiences serve multiple roles in this training system, including to help establish conceptual understanding for the relevance of targeted skills, raise awareness of situations and different phases of goal pursuit (e.g., encoding information versus redirecting attention following a distraction) where skill use may be beneficial, repeatedly and intensively practice skill use during these various phases, receive immediate and personalized feedback on skill use at such times, and support intentions and establish plans for utilizing skills in everyday life.

As in our previous intervention work, the primary training target in this system involves strengthening individuals' abilities to strategically apply self-regulation skills across settings and contexts. This is hypothesized to directly effect neural functioning, including neural networks involved with cognitive functions commonly impacted by brain injury, such as working memory and information processing [311]. To facilitate skill practice, the overall training is situated within a goal framework. Goals help guide skill application by providing a necessary point of reference for when individuals are dysregulated (i.e., when neurocognitive functioning poorly aligns with one's goal), and, thus, skill use is appropriate and may be beneficial. Training includes didactics and discussions on goal setting, self-regulation theory, and how to consider current states and behaviors in the context of one's goals. Trainers provide ongoing support and guidance to help increase trainees' *goal mindedness* and apply skills in game and personal life contexts.

Translation to Intervention Implementation and Delivery in Systems of Care

The considerations discussed in this chapter suggest important changes in the organization of existing systems of care. How integrated is the overall approach to the patient? The organization of care needs to be considered given the complex nature of cognitive dysfunction after brain injury and the approaches that are needed to improve functioning. The effective integration of any or all of the neural–cognitive processes and modulators illustrated in Fig. 1 is a particularly important determinant of overall cognitive functioning. Intervention approaches may need to foster the effective integration of these processes, and this may require integrating expertise across disciplines.

This may involve team members addressing and reinforcing common themes and issues that cross domains. Taking into account interactions between emotions and cognition is particularly relevant given the frequent co-occurrence of TBI and post-traumatic stress symptoms. Specific themes may be emphasized by multiple team members in different contexts and modalities, increasing the chances of accomplishing a therapeutic goal. For example, self-regulation skills may be learned best if applied in a range of situations. Individual practitioners may need to expand their range of expertise, for example, incorporating strategies that bridge cognitive rehabilitation with mental health, pain management, and substance abuse. Thus,

effective integration can require not only multidisciplinary but interdisciplinary and even transdisciplinary care.

Delivery of Care

Certain issues in the implementation and delivery for military veterans deserve special consideration. Treatment implementation and delivery methods need to be adapted to take into account issues related to geographic distribution of veterans, the "culture" of the military as well as community settings for post-military life, a high level of comorbidity with PTSD and other mental health conditions, individual goals after military service (e.g., educational or occupational), and more.

The wide geographic distribution of veterans creates challenges for treatment delivery and implementation. For example, one of the largest catchment areas for veterans returning from the combat in the Middle East spans thousands of square miles of Northern California, Nevada, and Hawaii, from oceans to mountains and desert as well as cities. The majority of veterans are not within easy travel distance to specialty medical centers. This limits the applicability of intensive on-site therapies and raises challenges to achieving integrated, interdisciplinary care.

Many of the cognitive, emotional, or behavioral problems that occur with TBI, even without deficits in other physical functions, have not been standard indications for inpatient or residential treatment. Expansion of inpatient or *residential* care programs may be necessary to provide access to integrated care in the *chronic* phases after injury.

Tele-rehabilitation

The use of tele-video technologies to extend the reach of neurocognitive interventions to those lacking direct access to rehabilitation holds tremendous promise. This is particularly relevant for the Veterans Health Administration given projections that over one million servicemen and women will transition to veteran status by 2020, many of whom will be returning to their rural communities with brain injury and related ailments [312]. Unfortunately, the majority of research and development on tele-rehabilitation has not focused on neurocognitive skills training but instead has emphasized assessment and diagnosis [313, 314]. Several aspects of tele-video communications, if not properly addressed as part of intervention development and design, can potentially undermine skills training (see Ng and colleagues [315] for an example). Of central importance is the difficulty with providing individualized guidance and support during training exercises over tele-video, potentially limiting how well skills can be developed and ultimately transferred to everyday goal pursuit. Thus, a critical goal for tele-rehabilitation research is addressing difficulties with effectively delivering training given limitations of remote interactions [316].

One potential means of providing remote training experiences of sufficient intensity and that allow for direct coaching on skill use is through using computer-assisted therapy tools, as in the training system we developed and previously described. In an initial pilot study, we adapted this training system for tele-video and assessed the feasibility of remote implementation as well potential training effects. In this adaptation, gameplay and modeling and observations of skill use are relayed in real time through use of an additional document viewer camera.

Preliminary findings from this pilot investigation were very encouraging [304]. Eighteen participants (15 veterans) with history of mild–moderate TBI and concurrent symptoms of PTS were assigned to remote training ($n = 8$) or treatment as usual (TAU) ($n = 10$) conditions. Groups were well matched across most demographic and injury characteristics, with the only notable exceptions being that TAU controls reported more symptoms of PTS and were slightly older than those undergoing remote training.

All aspects of the training protocol were successfully administered for all participants, with minimal technical difficulties. Participants were highly engaged with training, amassed signifi-

cant practice with skill application in game scenarios (participants practiced applying skills within game scenarios a median of 722 times and spent approximately 1/3 of total gameplay time engaging in self-regulation practices), and were able to benefit from remote coaching efforts to improve their ability to apply skills in their daily lives. As one illustration, a veteran who had difficulty understanding training concepts and identifying situations where skill use might be helpful was aided by the combination of coaching and gameplay experiences. His trainer utilized observations and experiences within the game world to increase the veteran's conceptual understanding of skills and as the basis for discussing how they could be extended to his personal life. For example, experiences with using self-regulation skills to manage reactions to customers' changing expressions within the game world were utilized to frame discussions about employing the same skills to better manage his frustrations with interacting with others at work. In addition, he was able to observe how his performance improved when he practiced self-regulation prior to starting a task, and these observations were utilized to discuss how this practice could be used before starting his workday or prior to beginning his daily commute. By the end of training, this veteran was able to identify a much broader array of game scenarios and personal contexts where skill use might be relevant.

Regarding objective benefits of the intervention, participants receiving remote training improved on a composite measure of complex attention, working memory, and executive functions (d = 0.64), whereas participants receiving TAU showed relatively minimal change (d = −0.07). Remote training participants also demonstrated improvements of a medium effect size on a functional real-world task (d = 0.42). On self-report measures, participants in remote training reported improvements of medium effect size on tasks requiring working memory (d = −0.55) and planning and organization (d = −0.56), whereas TAU showed minimal changes in these domains (d = −0.09 and −0.04, respectively). Self-perceived changes following training were also observed across a wide range of cognitive processes, notably with respect to attention and working memory and planning. Effect sizes for these changes were extremely large. As a preliminary test of the remote application of this training system, the objective and self-reported improvements together suggest that it is plausible that this training system may confer neurocognitive benefits. Furthermore, a training system that integrates coaching with intensive practice applying self-regulation skills in digital game scenarios and personal life is feasible to deploy for tele-rehabilitation.

Reaching Students "Where They Are"

Another important barrier is the divide between "medical care" and community. It is an unfortunate but well-recognized fact that many persons in need of services, in particular the community of younger veterans, are reluctant to seek medical help due to issues such as stigma [317]. Without adequate help, many of these veterans are unsuccessful in their efforts to re-integrate into the community, which frequently includes lack of success in post-secondary educational settings. Veterans are utilizing the GI bill at the highest rates since its inception, with over one million beneficiaries receiving an excess of $12 billion in payments in 2013 alone [318]. Yet, many student–veterans struggle in the academic setting, with the non-completion rate nearing 50% [319].

Students with TBI endorse a range of physical, cognitive, and emotional difficulties, including problems with attention, memory, and organization [139]. For military veterans, combat-related injuries are also associated with poorer and/or more inconsistent classroom attendance [320]—a factor critical for overall scholastic success. Students with TBI report having to work harder than prior to their injuries, but often lack appropriate tools and/or services to address their needs. This is particularly true for student–veterans who also often experience associated symptoms of PTS and chronic pain [319]. Innovative approaches to provide rehabilitation to support the long-term success of students with TBI are needed.

One potential means to increase access to rehabilitation for students is to integrate clinically informed skills training directly into the classroom setting. We recently adapted our experiential learning training system, which combined coaching and intensive skill practice across multiple contexts including digital game scenarios, for the college classroom setting. A major impetus for this adaptation was to provide students with TBI direct support with skill application on their academic goals and to overcome academic obstacles, including procrastination, environmental distractions, competing priorities, and academic anxieties, among others.

We completed a pilot investigation of this approach at a 4-year university, where we offered the intervention as a for-credit class in an attempt to increase access to training for college students. Participants included students with and without a history of TBI. Among the cohort of students with TBI ($n = 22$), we observed positive pre-post changes to performance on a computerized measure of working memory in the context of distractions ($d = 1.59$). Further, a subset of student–veterans with TBI who participated in neurocognitive assessments ($n = 9$) showed training-associated improvements on a composite measure of attention, working memory, and executive functions ($d = 0.42$). The magnitude of this latter change parallels results of our telerehabilitation pilot. Of note, changes observed following classroom training were selective to the training condition and were not seen in control conditions.

End of the semester feedback indicated that the training was acceptable and engaging and perceived to beneficial. Students reported success with applying skills to a range of academic tasks and challenges: 85% of students reported skills to redirect attention when distracted; 87% while working on homework/projects; 87% while studying; and 69% while attending lecture/class. Taken together, these data and experiences highlight that it is feasible to offer self-regulation training in a group format and that it is capable of engaging college-level students with TBI. Increasing access to neurorehabilitation by instituting a training-for-course-credit model may help combat issues related to stigma and, thus, get students the help they need and deserve.

Conclusions and Directions for Future Work

The effects of TBI on cognition are complex and have challenged clinicians throughout history, as well as deterred neuroscientists from pursuing studies in this "messy" area of inquiry. The complexity is compounded by combinations of physical and experiential injury, as well as other comorbidities. Much work will need to be done to better define effective therapies for cognitive dysfunction caused by brain injuries. Research and development along several key directions will be crucial.

Building a strong theoretical and scientific foundation will be valuable for guiding the development of new therapies. Understanding the brain systems that underlie the cognitive changes associated with brain injury should help in the delineation of targets in the rehabilitation of an individual with TBI. In particular, this knowledge will open the way for therapies that target biological systems and synergistically augment the beneficial specific effects of training.

Mechanisms of plasticity at multiple levels of neural functioning may be harnessed, but any neural changes will need to be sculpted to beneficially affect neurological functioning. Training provides a crucial set of methods to guide plasticity to achieve functionally integrated networks and improvements in behavioral functioning. For example, pharmacotherapy and other biological modification therapies may be integrated into rehabilitation to help augment learning, but much work needs to be done to define the specific effects of drugs at multiple levels of nervous system function, in order to best define combined behavioral-pharmacotherapeutic prescriptions.

Approaches that bridge the basic neuroscience of neural–cognitive functioning with the practical realities of clinical rehabilitation will be valuable in intervention development. It will be particularly important to consider the rela-

tionships between levels of functioning in order to maximize transfer and generalization of benefits.

Improved measures of the effects and mechanisms of interventions are sorely needed. Lack of adequate measurements limits intervention development. Measurement development needs to progress in at least two directions. First, biomarkers of the neural processes that mediate cognitive functions affected by brain injuries would be valuable for determining mechanisms. Cognitive neuroscience can serve as a foundation for development of these biomarkers, and new biomarkers of higher-order cognitive functioning are especially needed. These measurements will be crucial for elucidating mechanisms of the benefits (or lack thereof) for any intervention. Just as importantly, measurements that reflect functioning in ecologically relevant, real-life contexts are needed. Most tests of cognitive functioning, including neuropsychological tests and most cognitive neuroscience measures, are designed to isolate the processes of interest. On the other hand, the few functional assessment measures available are not linked in any clear way to the underlying neural–cognitive component processes affected by TBI. The development of ecologically relevant, neuroscience-driven interventions will benefit greatly from measurements that bridge neural–cognitive processes to real-world behavior.

Taking a long-term view on TBI in the context of the lifespan may lead to a major paradigm shift for the field. We will need to consider the enhancement of ongoing learning, recovery, and/or maintenance as a long-term goal of post-injury "brain health." Keeping in mind the benefits of bridging across levels of human functioning, across disciplines, and across the lifespan will significantly alter the emphasis of research and intervention development, expanding the horizons for improving cognitive functioning for individuals who have suffered brain injury.

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Mild Traumatic Brain Injury (mTBI) Affects the Family, Not Just the Injured Individual

Ronel Terblanche

Impact of Mild TBI on the Family

Overview

Mild traumatic brain injury (mTBI) is a significant public health concern. An estimated 70–90% of individuals who have received treatment for brain injury are classed as mTBI [1, 2]. The true incidence of mTBI is still unclear as not all individuals report to emergency departments following mTBI. The World Health Organization (WHO) task force suggested that in a civilian population, when taking into consideration hospital-treated mTBI as well as population-based surveys on self-reported mTBI, the true mTBI incidence could be higher than 600/100,000 [2, 3]. Since 2000, over 397,000 US military service personnel have sustained a TBI, the majority of these classified as mild [4]. Although the majority of individuals recover fully after an mTBI, there is a small percentage of individuals who continues to experience cognitive, somatic, and emotional changes. The exact reason for this is still not clear, and researchers have attempted to identify factors that could contribute to this delayed recovery.

Moderate and severe traumatic brain injuries (TBIs) have been studied by a large number of researchers, and the role the family plays in terms of recovery continues to be a topic of research. The effects of TBI on family relationships have been explored by numerous researchers [5–7]. Following a TBI, family members' responsibilities can include helping individuals manage activities of daily living, including daily tasks such as appointments and finances, as well as offering emotional support and helping to support socialization, thus playing a crucial role in reintegration following injury.

There is, however, very little evidence exploring the impact of mTBI on family reintegration in the current evidence base. To date, most of the mTBI research has focused on the individual, not on the significant impact physical, emotional, cognitive, and behavioral changes can have on family relationships after an mTBI.

Military, Mental Health, and Family Reintegration

Behavioral changes and relationship challenges have been long-standing concerns for military personnel returning from deployment. The risk of developing psychological difficulties following

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military deployment has been discussed within the literature, and according to surveys administered by the US military Mental Health Advisory Team (MHAT) [8], it is more likely that individuals will develop mental health difficulties as a result of stress within the family (this is related to difficulty with reintegration after deployment and difficulty with re-establishing roles/responsibilities). There is also a heightened risk of divorce and domestic violence in returning veterans [9].

It is also estimated that up to 19% of combat veterans returning from Iraq and Afghanistan go on to develop post-traumatic stress disorder (which can be either isolated or with an mTBI), and numerous studies have demonstrated the relationship between PTSD and problematic family functioning [10, 11], highlighting the multiple factors that can interfere with reintegration into home life after deployment and sustaining a life-changing, sometimes "invisible," injury.

As there is a significant overlap between somatic, cognitive, and psychological symptomatology after an mTBI, it is important to understand the impact psychological changes following such an injury could have on family dynamics, despite the lack of empirical evidence to support this notion.

Individuals with an mTBI can have a range of cognitive, physical, and psychological symptoms, and in most cases, these symptoms resolve promptly. However, a subset can experience persistent symptoms post-3 months that can create unique treatment challenges; emotional, somatic, and social interaction changes can all affect the family dynamic [12]. Hyatt's study [12] specifically investigated service members returning from a deployed setting after sustaining an mTBI. The injured individual may express stress in the form of anger, depression, and anxiety, and sometimes it can be perceived by family members as a personality change. Without prompt recognition, understanding, and intervention, mTBI and its longer-term consequences could have a major impact in terms of reintegration into the family.

Evidence from the TBI literature, specifically a study conducted by Wood and Yurdakul [13], highlighted a change in marital status following head injuries of varying degrees/severity, specifically, that almost 50% of individuals were divorced or separated after the head injury (this follow-up was conducted on average 8 years post-injury), identifying a potential breakdown in family relationships following TBI. Poor family support and lack of cohesiveness might also be contributing factors to work and community integration after a TBI, indicating the role of the family to support better outcomes after TBI [14].

When evaluating whether family members receive input or support to prepare themselves for the caring role they potentially have to play, it appears that despite the rehabilitation teams' best efforts to educate and prepare families, many report feeling overwhelmed and poorly equipped to provide for the individual's complex long-term needs [15, 16]. Research indicates that a family's ability to cope in the face of stressors influences the quality of support they can provide to the injured individual [17].

mTBI and Family Integration

When examining the potential relationship between family functioning and community integration, Sady and colleagues [18] found, specifically with mild to moderate TBI, that having a family that has a healthy dynamic prior to injury may be associated with higher levels of independence with personal and domestic activities of daily living, highlighting the importance of family support to facilitate better outcomes after both mild and moderate TBI.

Family intervention is not an area that has been well researched within the field of mTBI; however, Kreutzer and colleagues [19] attempted to bridge this gap by examining family intervention after TBI with the use of the Brain Injury Family Intervention (BIFI), which is a structured treatment approach, focusing on those areas most identified as requiring support by both the family and TBI individual; within this study, a subsample was mTBI individuals. This study highlighted that the treatment approach (focusing on education, skill building, and emotional support) was successful in reducing perceived barriers to

accessing other services in the post-acute phase as well as meeting the needs of the family members set out at the start of the intervention. It is, however, important to note that this study did not have a control group, and numbers of participants were low. It does, however, provide support to the importance of family intervention following mTBI.

Bay and colleagues [20] found that individuals with an mTBI who experienced self-perceived low levels of belonging and a poor valued fit and involvement with others were more likely to have self-reported limitations with emotional control and social interaction, and these individuals also lacked confidence, highlighting the potential relationship between social support and recovery after mTBI. The study also discussed that the focus of treatment, both for the individual and family involvement, should also include psychological work for the individual to regain a sense of belonging, as this might lead to improved psychosocial outcomes. This is further supported by Bell and colleagues [21] who found that focusing on symptom management alone will hinder psychosocial and, in turn, overall recovery.

Laudau and Hissett [7] conducted a qualitative study where they examined the loss of self and identify ambiguity and the impact of this on the family following an mTBI. Individuals following mTBI described changes with their self-image, a reduction in confidence, and generally a loss of their sense of self, demonstrating the complexity of this injury. It is also likely that, if one member of a family structure's roles and identity are in question, this could have a significant impact on the family system itself. Laundau and Hissett [7] go on to further discuss that after an mTBI, it is important that the individual's boundaries within the family should be discussed and identified, especially the emotional changes the individual may be experiencing, thus involving both the family and the mTBI individual in the rehabilitation process. Changes in socialization, emotional status, and perceived functional performance can impact on how the individual interacts with the family, and, with a change in these skills, family dynamics can potentially change. Returning to "normal" is not always realistic, and the focus has to be shifted toward developing/creating the person they want to become; therefore, the family has to work together to move toward finding "their new joint reality," which will reduce ambiguity and false hope.

Hyatt [12] identified, by using a grounded theory methodology, which supports the conclusions of Landau and Hissett [7], that finding the "new normal" appears to be one of the main foci of family reintegration, and three themes were identified: (1) facing up to the service member's unexpected return home; (2) managing unexpected changes in the family routine, which can include having to take on more of a caregiver's role; and (3) "experiencing mismatched expectations," such as unrealistic views of the mTBI individual's functional abilities (by both the individual and family member) and adjusting to new expectations for the family and the likely shift in relationships. The study also found that longer marriages (>10 years) appear to adjust faster to changes following injury and that there were also other challenges when returning from deployment with an mTBI, such as changes to normal family routine (delayed [and unexpected] changes), understanding how to fit injury-related difficulties into the family dynamics, and managing and resolving misaligned expectations.

Lefebvre and Levert [22] also attempted to capture the experiences of individuals and their families after sustaining an mTBI. Themes that were identified through the focus groups in this study, related to treatment and recovery, were, firstly, the need for expert, early intervention. They also reported that there was a requirement for clear, accurate information and that a lack of information can have devastating consequences for the individuals who develop chronic difficulties and for their family members and friends. The participants in the focus group also agreed that, because their mTBI symptoms did not resolve within the timeframes many professionals acknowledged and reassured, their symptoms were likely exacerbated by the lack of understanding of why their symptoms have not resolved.

Faced with difficulties that they did not fully comprehend, combined with the inability to

resume their pre-injury functional level, this could potentially lead to a reduction in self-esteem and confidence. Most family members felt the need to support the mTBI individual but did not feel they had tools to do this effectively. Ongoing problems can also lead to a requirement to change the family dynamics, with others taking on more and different roles than pre-injury. There appears to be consensus from participants that a lack of support for the family in the acute phase of recovery is a problem, as most of the attention is focused on the individual who had sustained an mTBI, rather than being inclusive of the family. This ties in well with Gillen and colleagues [15] and Hall and colleagues [16] who found that despite some input in the acute setting, families still feel ill-equipped to deal with the TBI individual on return home from the hospital, supporting the notion that family support and education can help support functional recovery and facilitate family reintegration of the mTBI individual.

Current Military Information/ Treatment Programs

Within the US military, the Defense and Veterans Brain Injury Center (DVBIC) has developed a Family Caregivers Guide to help support the transition from "family member" to "caregiver" after a service member sustains a TBI. Although this guide mostly focuses on moderate and severe TBI, some of the information can be generalized to the mTBI population.

This guide/booklet aims to encapsulate some of the key themes identified through research, including the caregiver/family member in the rehabilitation pathway, providing them with clear, accurate information, both in visual and written format, as well as contact details of clinicians that are a part of the holistic treatment approach. It is also acknowledged in the booklet that a key component of changing roles and relationships following a TBI is to ensure that the caregiver looks after their own health and well-being, and practical approaches, tips, and ideas are provided along with contact details of where support can be obtained [4].

In the United Kingdom, the charity, Headway, has written a booklet on "Caring for Someone with a Brain Injury," again with the focus on more severe TBIs [23]. The Defense Medical Rehabilitation Centre Headley Court, as part of their mTBI service, designed a one-page leaflet for relatives, explaining what an mTBI is and what they can expect following an mTBI. Family members are also encouraged to attend sessions with the injured service person to help support reintegration and educate the family member on how they can support them.

Summary of Intervention to Support Family Reintegration

There is clearly a requirement to ensure family education and support is offered to best enable the mTBI individual to reintegrate into the family system. This intervention should aim to include some of the recommendations, as extrapolated from the evidence (as discussed in this chapter):

- *Requirement for early, expert intervention.* Early assessment, education, and treatment of the mTBI and other difficulties following the injury are vital to symptom recovery.
- *Provision of clear, accurate information to both the mTBI individual and the family*. This can take the form of leaflets but should also include face-to-face sessions with family members to help prepare them for their role in the recovery process.
- *Support from clinicians to help with improving mTBI difficulties*. This is essential, but the clinician should aim to use a holistic approach. Sessions should include, where possible, the family in the rehabilitation process alongside the biopsychosocial aspects of care.
- *Collaboration and joined-up care with inclusion of a family component to form part of the service*. Following an mTBI, individuals report that it would be beneficial to their recovery if there was collaboration between all healthcare professionals as well as utilizing both physical and psychological treatment approaches (holistic) and working toward

improving and protecting family relationships. Therefore, considering the biopsychosocial aspects of care is deemed as essential. Persistent symptoms may subsequently require the whole family dynamics to be altered or shifted, with some family members taking on more responsibilities than before the injury.

- *Reconstructing a new sense of self*. Supporting individuals to adjust to how they view their injury, themselves, and others is vital to the recovery process; what might initially be seen as a loss or challenge can become something more positive (gains after the mTBI) – personal growth experience. A key concept to facilitate post-traumatic growth is for the individual and family to work together to accept their current situation and the changes since the injury (growing "together"). Support to address expectations that differ and help working toward acceptance of their "new" normal should be considered, and mTBI intervention has to focus on both the mTBI individual and the spouse/family members.

Conclusion

mTBI remains a complex condition to treat as the symptoms are multifaceted. The longer-term consequences and changes as a result of an mTBI can have a detrimental impact on not only the mTBI individual but also on family relationships. This may be due to the perception by the spouse of personality and behavioral changes within the individual, such as increased anger, frustration, anxiety, and loss of motivation, self-esteem, and confidence. This is likely linked to the impact the cognitive and physical sequelae are having on the individual's sense of self and their own adjustment process. These symptoms could interfere with a couple's communication and relationship and, thus, possibly challenge martial satisfaction.

Using a holistic treatment approach early after injury, involving the family within the recovery process, and supporting healthy family dynamics is likely to support improvements following an mTBI. Finding ways to support the individual and family to manage emotional distress and accept lasting changes after the mTBI may be key to post-injury family reintegration and improved socialization.

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Pediatric Concussion Diagnosis, Management, and Rehabilitation

Tina L. Samuel and Karen M. Barlow

Definition

Surprisingly, there is considerable controversy about the definition of concussion [1, 2]. Concussion in general is considered to be part of the spectrum of mild traumatic brain injury (mTBI). Although concussion is usually at the milder end of the spectrum of mTBI [3], sport-related concussion (SRC) is of particular interest because of the risk of repeated concussion and subclinical concussive events and because concussions are often occurring in different physiological milieus (e.g., lactic acidosis, depletion of energy reserves, etc.). For these reasons, as well as increasing concerns about the potential for long-term consequences of sport-related concussions, many studies focus on the sport-related concussion population alone [4].

mTBI is a traumatically induced physiological disruption of brain function [5, 6]. The alteration in brain function is determined clinically. If there is a loss of consciousness (LOC), this should not exceed more than 30 minutes. Similarly, post-traumatic amnesia should resolve within 24 hours. There should not be any focal neurological signs, and the Glasgow Coma Scale (GCS) should be between 13 and 15. Concussion has also been defined as a biomechanically induced alteration in brain function due to resultant complex pathophysiological processes [7] but should fit within the mTBI parameters. If not, a more serious injury or alternate diagnosis should be considered. Standard structural neuroimaging studies are usually normal. If contusions or small hemorrhages are seen and the clinical parameters for mTBI are satisfied, these injuries are usually referred to as *modified* mild TBI.

Concussion/mTBI can be caused by a direct blow to the head, face, neck, or elsewhere on the body with an "impulsive" force transmitted to the head. The short-lived impairment of neurological function is usually of rapid onset; however, in some cases, symptoms and signs may evolve over a number of minutes to hours. There remains considerable debate about the minimum number of symptoms required to satisfy criteria for neurological impairment [8] and also around the delay of symptom onset. Overall, it is reasonable in clinical practice to assume onset of symptoms within 2 to 3 days [8]. However, some patients may not have the above factors medically documented during initial assessment. In such cases, it is essential to consider the symptomatology that can suggest the existence of an mTBI. Typically, these symptoms can present for varying lengths of time and can spontaneously resolve. However, sometimes they can evolve

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over weeks to months and can lead to prolonged impairments in neurocognitive function.

Epidemiology

TBI is one of the most common neurological conditions and particularly affects children, with males being at the highest risk [9]. About 823.7 per 100,000 people per year require medical attention in the emergency department (ED) in the United States for a TBI, and about 75–90% are mTBI [10]. As many persons with mTBIs never reach medical attention or seek care from community clinics, the true incidence is likely to be much higher [11].

The incidence of concussion may be increasing, although it is likely that this is mainly due to increased reporting. The number of sport-related concussions (SRCs) and recreation-related concussions seen in the ED has increased rapidly over the last 15 years, especially since changes in concussion legislation beginning in 2009 [9]. For example, between 2001 and 2012, the numbers of SRCs seen in the ED increased by more than 50%; and, although males (ages 0 to 19 years) remain at the highest risk for TBI and concussion, the most remarkable increases have been seen in 15- to 19-year-old girls, where the incidence has increased by 210% [9, 11], and in children younger than 4 years of age [12]. Similarly in Canada, the number of sport-related brain injuries visiting the ED has also increased by 46%; here, the largest increases have been seen in younger children (ages 0–9 years) where numbers have increased by 78% [13].

The etiology of concussion is dependent on age and environment as well as pre-injury psychosocial and behavioral characteristics. Risk factors for concussion and mTBI are shown in Table 1. Most young children sustain injury in falls (about 78%); even in these young children, the environment plays a role (e.g., more injuries occur in the playground compared to the garden, presumably due to the presence of climbing equipment) [14–17]. As children age and become more active and adventurous, the incidence of SRCs increases [12].

Table 1 Risk factors for sport-related and non-sport-related concussions

Sport-related concussion	Non-sport-related concussion
Age and gender	Age and gender
Choice of sport participation and style of play	Genetics/epigenetics
Coaching, rules, and refereeing	History of learning disabilities, attention-deficit/hyperactive disorder, and/or anxiety
History of learning disabilities and attention-deficit/hyperactive disorder	History of migraines and/or previous posttraumatic headaches
History of migraines and/or previous posttraumatic headaches	Injury severity
Injury severity	Preexisting neurologic and psychological conditions
Previous concussion, especially with slower recovery after each successive concussion	Previous TBI/stressful life event
Remote concussions	

During 2014–2015, approximately 94% of all youth sport-related brain injuries seen in EDs across Canada were concussions, with the highest proportion of injuries among 10- to 14-year-olds (29%) [13]. The sports with the highest incidence of concussion are "contact" sports, including ice hockey, American football, and rugby [7]. It should be noted that not all concussions are reported, and there has been considerable work over the years to encourage athletes to report. Some players may not report concussion because they do not believe in the extent/seriousness of the condition, do not wish to stop playing, or may not recognize that they have sustained a concussion. Factors in their decision-making include the fear of losing their position, appearing weak, letting their teammates/coaches/parents down, and jeopardizing their future sport career. Education has tried to target these fears, emphasizing that it is better to recover from the first concussion than to compound one concussion with a more severe concussion in a brain that has not yet recovered and risk a prolonged recovery. Of concern, subsequent SRCs tend to occur with less forceful events and result in higher symptom loads.

Pathophysiology of Acute Concussion

In childhood, concussion is occurring during a rapid period of brain development and maturation that is determined by age, sex, and genetic influences. A child's brain has different mechanical (i.e., resistance to strain, lower neck strength in comparison to head size) and compositional properties than an adult (i.e., increased water content, increased synaptic density, and decreased myelination), leading to the increased translation of acceleration-deceleration forces. Thus, there is an increased potential for shear injury and brain tissue displacement during a traumatic event, which is dependent on age and physiological development.

A TBI begins with an insult to the brain which results in complex pathological processes and enzymatic cascades. The biomechanical force associated with concussion results in a movement of the brain within the skull and can occur with or without direct forces being applied to the head. Forces can be linear (i.e., with direct impact), but are more likely to be rotational. These rotational acceleration-deceleration forces cause shear strain within the brain tissue itself and are maximal at the junction between tissues of different densities [18]. Sometimes, the brain collides with the inside of the skull resulting in deformation of brain tissue, which may result in contusion(s) and coup-contrecoup injury. Injury occurs when the deformation forces exceed the structural limitations of the tissue (e.g., blood vessels, neurons, glia, etc.). As the gray and white matter have different water contents and densities (which change throughout brain development as myelination occurs), shear stresses occur on the axons, blood vessels, and oligodendrocytes as they cross areas of different densities.

During shear stress, forces cause the cellular membranes to leak, known as mechanoporation, resulting in cellular process disruptions. If the forces are large, traumatic axonal detachment (focal or diffuse axonal injury [Wallerian degeneration]), blood-brain barrier disruption, and vascular injury may occur [19–21]. When traumatic neuronal injury occurs, there is an indiscriminate release of neurotransmitters, activating enzyme pathways and other cellular processes. This indiscriminate release of neurotransmitters, especially glutamate, begins a process called excitotoxicity. With uncontrolled release of glutamate, the ensuing neuronal activation is excessive, and there is an increase in both cellular metabolism and the generation of multiple reactive oxygen species (free radicals) [22–24]. Calcium dysregulation after TBI also plays an important role in secondary cell damage and cell death. All of these processes require energy, and if supply cannot meet demand, further cellular damage can follow – often referred to as secondary injury. Many injured cells will repair and resume normal functioning; some neurons or glial cells will not. This is dependent on the severity of the insult and injury, as well as the person's innate response to injury. Damaged or dead neurons are not all closely grouped but may be spread throughout the brain in what is called diffuse axonal injury. The distribution of the injury (focal or diffuse) depends on the primary insult, the biomechanical properties of the brain, the size and propagation of force waves through the tissues, and the resultant location of stress points.

Less is known about the long-term pathophysiological recovery processes following TBI, especially in children where the injury can disrupt normal developmental processes, such as changes in receptor expression, synaptic pruning, dendritic morphogenesis, and myelination. There is also strong pathological evidence for a prolonged immune response in TBI, with identifiable microglial and astrocyte activation and microvascular changes in the blood-brain barrier years after injury. Pro-inflammatory processes are intended to clear the central nervous system of potentially harmful substances and cellular debris. Anti-inflammatory processes follow this, performing reparative and regenerative functions. However, an unbalanced or prolonged inflammatory response in either the pro- or anti-inflammatory direction can be harmful, leading to excessive cell death and glial scar formation, and may contribute to poorer long-term outcomes [25–30].

Diagnosing a Concussion

Concussion is a clinical diagnosis. Successful management relies on the ability of the public to recognize a potential injury and healthcare providers to make an accurate diagnosis. This can be especially challenging in concussion, where late presentation to medical attention is common.

Loss of consciousness (LOC) is easy to associate with a concussion, but occurs infrequently. Indeed, only 10–20% of children have experienced an LOC when they present to the emergency department with a concussion [31], and it is reported in 9% of SRCs [32]. When LOC does occur, it is usually brief. In our experience, if LOC lasts longer than 5 minutes, a more severe injury or alternate diagnosis should be considered. Instead, in children presenting to the ED, the commonest symptoms are those of confusion/disorientation (61%), headache (85%), and dizziness (60%) [31]. In SRC populations, the types and frequency of symptoms encountered are similar, with headache (86%), dizziness (67%), and confusion (59%) being most commonly reported [32]. Certain symptoms, especially headache and emotional dysregulation, may have a delayed onset and only occur several hours to a few days after the event.

Symptoms following a concussion load onto four principal domains: physical, cognitive, emotional, and sleep related. *Physical symptoms* include headaches, nausea, vomiting, dizziness and/or balance issues, blurred/double vision, fatigue, lethargy, numbness/tingling, photophobia, and/or phonophobia. *Cognitive symptoms* may include initial confusion and disorientation, followed by difficulty with concentration, psychomotor slowing, and problems with memory (usually short term) and attention. *Emotional regulation* difficulties can occur within hours although they more commonly evolve overtime. There may be quite remarkable emotional dysregulation acutely, with a very upset and anxious child who is difficult to soothe and calm. More usually, feelings of sadness and anxiety occur late with or without emotional liability. The person is often more quick to anger or show greater disinhibition compared to pre-injury levels. Younger children may be more irritable and oppositional and be more prone to cry than before the injury. *Sleep-related problems* are common complaints before the injury; however, early after the injury, there is often increased drowsiness and lethargy, whereas several days later there is an inability to fall asleep and more frequency to wake at night. None of these symptoms are specific for concussion [33]. They can be due to other factors, such as an extracranial injury, pre-existing emotional state, and a psychological reaction to injury. It is worth noting that these symptoms can also be overlooked in the presence of more overt physical injury (i.e., orthopedic or spinal cord injuries).

Most post-concussion symptom questionnaires capture these symptom complaints (i.e., post-concussion symptom inventory [PCSI], Rivermead, post-concussion symptom scale [PCSS]) and are useful in the first few weeks to months to help track the recovery progress. Various tools and apps have been developed to help recognize a concussion and track the early recovery processes. However, none of these tools should be used as a stand-alone method to diagnose concussion/mTBI, and concussion remains a clinical diagnosis.

History and Examination in the Acutely Concussed Child

Acutely, the history and examination is focused on immediate resuscitation and evaluation to detect a severe injury which may require urgent neurosurgical treatment or intensive care admission. It is not uncommon for a person with an mTBI to look very unwell in the first few minutes after the insult. A rapid evaluation at the scene of the injury may lead to the activation of emergency and urgent care services. The Sport Concussion Recognition Tool [34] or the Concussion Recognition and Response app [35] for smartphones is useful for coaches, parents, and teachers to help recognize concussions and determine the acute "on field" management. Higher-energy injuries, children with LOC, recurrent vomiting, severe acute symptoms,

seizures, focal neurological deficits, and/or atypical features should be evaluated in the ED. See Box 1.

Box 1 Acute Symptoms and Signs at the Sideline That Require Activation of Emergency and Urgent Care Services

- High-energy injury
- Loss of consciousness
- Recurrent vomiting (more than twice)
- Severe acute symptoms
- Seizure
- Focal neurological signs
- Suspected neck injury
- *Anticoagulation therapy or clotting disorder*

A description of the injury should be obtained early as higher-energy insults are more likely to be associated with complications. A persistent alteration in the level of consciousness, suspicion for an open or depressed or basal skull fracture, worsening headache, irritability, and a large boggy hematoma are risk factors for a more serious injury and may warrant further investigations with CT or MRI. Healthcare providers are encouraged to use a validated clinical decision rule (such as the Canadian CT Head Rule) to identify children at risk for intracranial injury. Most decision rules combine a variety of risk factors to determine need for brain imaging including age <2 years old, repeated vomiting, prolonged LOC, severe mechanism of injury, severe/worsening headache, amnesia, non-frontal scalp hematoma, GCS <15, or clinical suspicion for skull fracture. As a neck injury may present in a similar way or co-occur with a concussion, clinical evaluation for a significant neck injury is commonly performed. If there is severe midline tenderness, a high-energy injury, and/or signs of a cervical radiculopathy, C-spine imaging should be performed.

Children are not always easy to assess. Young, scared children in pain may not be fully aware or able to articulate their symptoms clearly. A more overt extracranial injury may detract or mask the symptoms of a concussion. Factors that might make the clinician's evaluation more difficult and/or less reliable are shown in Box 2. Young children with head injury, particularly those with an injury that is inconsistent with the history or with retinal hemorrhages, should be assessed for child abuse. See Box 3.

Box 2 Factors That Might Make the Clinician's Evaluation More Difficult and/or Less Reliable

- Age less than 3 years
- Alcohol and/or drug use
- Preexisting significant learning difficulties
- Language barrier
- Significant extracranial injury
- *Spinal cord injury*

Box 3 Worrisome Signs Requiring Further Investigations

- Disturbance of consciousness or deteriorating conscious level
- Evidence of skull fracture or basal skull fracture such as Battle's sign, raccoon eyes, hemotympanum, cerebrospinal fluid otorrhea or rhinorrhea, or cranial nerve injury
- Evidence of cervical spine injury
- Focal neurological signs
- Evidence of vestibular dysfunction (e.g., nystagmus, abnormal head thrust test, or Dix-Hallpike maneuver)

Evaluating for Cognitive Disturbances

Children and adolescents who present to the ED after sustaining an mTBI often have lower psychomotor speeds and reaction times. Standard concussion assessments (i.e., paper and pencil tests) are less useful in measuring

these aspects of cognitive performance. As an alternative, computerized cognitive testing may be desirable because it can detect early cognitive problems and provides a measurement of reaction times and processing speeds [36] and may help guide management. Early studies suggest that computerized cognitive testing is feasible in the ED and can be rapidly completed without interfering with the clinical flow of the ED, without harm to the patient, and whose results may prognosticate outcome (sensitivity of 93%) [36–38]. However, further work is needed to validate the usefulness of testing in this clinical setting [37].

Useful Tools for the Clinician

- *The Standardized Assessment of Concussion (SAC)* is helpful in identifying a concussion in the early acute post-injury period [7]. It is a brief assessment of some aspects of cognition, such as orientation, concentration, and immediate and short-term memory, and takes about 5–7 minutes to perform [39]. It has a sensitivity of 80–94% and specificity of 76–91% on the day of the injury.
- *The Child Sport Concussion Assessment Tool (ChildSCAT5) for children aged 5–12 or the Sport Concussion Assessment Tool (SCAT5) for athletes aged 13+* combines the SAC, the post-concussion symptom scale (PCSS), and the modified Balance Error Scoring System (BESS). An app is available. This assesses and tracks cognitive, clinical, and balance performances post-injury and also provides advice for the athlete and parent. Attempts have been made to increase the accuracy of the SCAT by performing baseline testing; however, the utility of baseline testing in children has not been validated and is controversial.
- *The Acute Concussion Evaluation (ACE) and ACE-ED* questionnaire may be used for assessment on the day of injury or the following day. This combines a brief clinical history with a short symptom checklist and offers advice on early management, follow-up, and medical coding information.
- *The Balance Error Scoring System (BESS)* is an objective measure of static postural stability and is often used in the early stages following a concussion, especially in SRCs and athletes, as good balance is essential for most sporting activities. It can be performed in nearly any environment and takes approximately 10 minutes to conduct. It consists of three different stances on two different surfaces – both a firm (ground) and foam surface. The child should place each hand on the iliac crests and then close his/her eyes and maintain a consistent foot position depending on the stance. Each of the trials is 20 seconds in duration:
  - *Double-leg stance*: Feet are flat on the testing surface approximately pelvic width apart.
  - *Single-leg stance:* Child is to stand on the nondominant leg with the contralateral limb held in approximately 20 degrees of hip flexion, 45 degrees of knee flexion, and neutral position in the frontal plane.
  - *Tandem stance:* One foot is placed in front of the other with heel of the anterior foot touching the toes of the posterior foot. The nondominant leg is in the posterior position.
  - *Scoring:* The examiner is to count the number of errors (deviations) from the proper stance only after the individual has assumed the proper testing position. Such errors include moving the hands off the hips, opening the eyes, stepping/stumbling or falling, abduction/flexion of the hip beyond 30 degrees, lifting the forefoot/heel off the testing surface, and remaining out of the proper testing position for greater than 5 seconds. The maximum total of errors for any single condition is 10. If a subject commits multiple errors simultaneously, only one error is recorded. The information obtained from this clinical balance tool can be used to assist a clinician's decisions about return to activities when compared to previous assessments (at baseline, time of injury, etc.). The test should be used with a standardized symptom scale checklist or inventory.

- *The King-Devick test* is a combined visuomotor/visuospatial and cognitive task that can be performed easily on the playing field sideline as well in the ED. Here, patients are asked to read numbers on a series of cards from left to right as quickly as possible but without making any errors. After completion of the demonstration card, patients read each of the three test cards in the same manner. The times required to complete each card are recorded in seconds using a stopwatch. The sum of the three test card time scores constitutes the summary score for the entire test (K-D time score). Error scoring is based on the number of errors made in reading the test cards and misspeaks on numbers without immediate correction.
- *The Concussion Clinical Prediction Rule* may be able to assist in the assessment of the child presenting to the ED within 24 hours of a concussion by helping to predict who may be at risk of prolonged post-concussion symptoms [40]. For children at high risk of persistent symptoms, it has a negative predictive value of 70% and positive predictive value of 60%.

Diagnostic Studies

Routine laboratory or brain imaging investigations have little role in the clinical diagnosis. Routine CT or MRI scans contribute little to concussion evaluation and should be employed only whenever an intracerebral or structural lesion is suspected. Nevertheless, although CT imaging is usually normal, MR imaging performed acutely in children presenting to the ED with mTBI demonstrates evidence of structural injury in approximately 14% of cases [41]. Abnormalities on imaging do not predict poor outcome in concussion and do not have a clinical role at this point. Special MR, such as susceptibility-weighted imaging, arterial spin labeling [31], and diffusion tensor imaging, has been used in research studies, but as yet has little to offer in the management of patients and cannot be recommended other than in a research setting [42].

Management

Any athlete/player with a suspected concussion should be removed from play, medically assessed, and monitored for deterioration and should not drive a motor vehicle until cleared to do so by a medical professional. Athletes diagnosed with concussion should not return to sport participation on the day of the injury or the first few days after the injury to avoid reinjury or the worsening of underlying symptoms.

The majority of children with concussion seen in the ED are discharged home. In our local cohort studies, less than 5% of children require admission or prolonged observation in the ED [43]. After assessment and evaluation, it is safe to have the child/adolescent observed at home under the supervision of a responsible adult if their mental status is now normal and there is no indication for admission (Table 2).

An important part of the initial management is to provide reassurance to parents/caregivers that the outcome from concussion in the majority of individuals is very good and that symptoms are likely to resolve within a few weeks for the majority of children. The family should be given instructions about when to return to the ED for further help (Box 4). Having followed those guidelines for further investigations and criteria for discharge, it is rare for children to return to the ED for a serious medical/neurosurgical condition.

Table 2 Criteria for hospital admission or prolonged period of observation in the emergency department

Persisting disorientation or altered mental status	Imaging and admission
Abnormal neuroimaging	Admission for observation, neurosurgical consult
Preexisting neurological condition (e.g., autism)	Consider longer period of observation
Risk of bleeding (e.g., hemophilia, warfarin)	Imaging required and consult hematology
Previous neurosurgical procedure (e.g., ventriculoperitoneal shunt)	Consider imaging and consult
No reliable observation at home	Admission

Box 4 Reasons to Return to the Emergency Department After Discharge Following a Concussion

- Cerebrospinal fluid or bleeding from the ear or nose
- Confusion or altered mental status
- New neurological signs (e.g., blurred vision or slurred speech)
- Seizure
- Severe progressive headache
- Symptoms to suggest raised intracranial pressure (e.g., headache, recurrent vomiting, decreasing level of consciousness)

Healthcare providers should encourage a gradual return to regular daily activities with *temporary* physical activity restrictions and encourage follow-up with their primary care provider. The following can be helpful and are encouraged:

1. A discharge summary prepared for the primary care provider
2. Written and verbal injury advice given to the patient and parent/guardian covering as follows:
   (i). Normalizing symptoms (education that current symptoms are expected and are common after an injury event) along with expected outcomes.
   (ii). When to return to the ED, including the symptoms or signs to look for (RED FLAG symptoms, Box 4).
   (iii). Lifestyle advice to assist recovery and reassurance about expected positive recovery; include information about the gradual return to school classes and physical activity.
   (iv). Follow up by the family physician to help monitor progress and ensure specialty referral can be made if indicated.

There are several consensus-based recommendations from organizations like the Ontario Neurotrauma Foundation, Centers for Disease Control and Prevention, and American Academy of Neurology that can provide useful tips and tools for management. It is important to recognize that the use of such guidelines requires the implementation of a developmental approach to the understanding of a child in their everyday context [44], instead of being an application or "downsizing" of an adult model. They require healthcare providers to examine preexisting and/or environmental factors that may elicit or indicate the potential development of lingering symptoms which may impact the recovery process [45–47].

Rest

The first initial step in management is to prescribe rest and restrict certain activities in order to avoid repeat injury or worsening of symptoms. Ideally, the patient should rest (both physically and mentally) at home to avoid strenuous activity for the first 1 to 2 days after their injury. Patients and their families should be instructed to limit computer time, video games, texting, and light reading until the second or third day post-injury. Physical activity is restricted, although walking and light aerobic exercise (without perspiration) is encouraged, as tolerated by the child/adolescent. A graduated approach is suggested to increase cognitive and physical load simultaneously [48]. It is sometimes difficult for an active child/adolescent to rest, so some light cognitive activities are helpful during the first 2 days post-injury. After this period, they can gradually increase their activities in moderation. *Prolonged rest is not recommended* [49].

"Return-to-Learn" Recommendations

Ideally, a child should return to normal cognitive activities before completing all the return-to-learn steps. It usually takes less than a week or two to get back to normal activities at school. On the second or third day, slowly begin to increase cognitive load and associated stressors to improve concentration, memory, and sensitization to light/noise. Social interaction is also encouraged at

this time, such as engaging with one friend at a time (i.e., play dates for younger children or a telephone call). Gentle activities like light reading and screen time with personal electronic devices for 15- to 20-minute sessions at a time can be started. By the third or fourth day, the child/adolescent should go back to school for half-days initially and work up to a full day of school. It is preferred to have them start attending their least stressful classes and having them participate in class work and socializing with their peers. They should be gradually reintegrated and resume full workloads at school, including homework and examinations/tests. Usually, aerobic exercises are started around this point. A minimum of 24 hours is recommended per step, and graduation to the next level is based on how well the child/adolescent tolerates the activity. If they are not tolerating their symptoms or the activities are making such symptoms worse, have the child either reduce the duration of activity or move back to the previous step.

Mood changes and anxiety can be common during recovery from an mTBI. Many school-age children and adolescents worry about failing at school, not being active, and feeling left out. This may make symptoms worse or prolong recovery. Social isolation can be reduced by returning to school and participating in activities as much as possible. Clinicians should encourage open communication between the family and the school to facilitate short-term educational modifications in the first few weeks. Some children may require help from a counselor to help alleviate the stress associated with recovery. Long-term educational modification is not necessary for the vast majority of students and should be provided only with involvement of specialized services, such as educational or neuropsychological advice.

"Return-to-Play" Recommendations

Once the child/adolescent is attending school regularly and tolerating their school day, they can increase their light aerobic exercise. The purpose of the incremental increase in exercise is to increase the heart rate and physical endurance without marked symptom exacerbations. We do not recommend resistance training, weight lifting, or activities which contain head/body contact during this time. Eventually, sport-specific training and exercises are initiated, usually for a shorter period of time (e.g., 20–30 minutes twice a day). This helps to improve strength and flexibility needed for the particular sport as well as endurance. Afterward, non-contact drills and training activities can be started.

Activities can be started with a teammate or friend initially. Resistance training, weight lifting, and "beginner-level" sport-specific skill can begin while avoiding checking, heading the ball, tackling, or live scrimmage-type training activities. Skill levels can be increased overtime, as tolerated, to promote exercise, improve coordination, and restore confidence along with the ability to handle a full cognitive load.

A minimum of 24–48 hours is recommended per step based on how well the child/adolescent tolerates the activity. If they are not tolerating their symptoms or the activities are making such symptoms worse, have the child either reduce the duration of activity or move back to the previous step. These recommendations may take a few days or 1–2 weeks depending on the progress of the child/adolescent's recovery. Once the child/adolescent is symptom-free, medical clearance from a family physician or healthcare provider experienced with treating concussions is required before returning to full-contact or controlled training activities and game play. After medical clearance is attained, the child/adolescent can participate in normal training activities without restrictions; and when ready, they can return to full competitive activities.

Post-concussion Syndrome

Post-concussion syndrome (PCS) is a constellation of clinical symptoms that persist for 1 month or longer following the injury [50]. In the first 2 weeks following the injury, many children show a rapid resolution of symptoms. However, 30–50% of all children with mTBI remain symptomatic at 1 month [31, 40, 43, 50]. These children are often

Table 3 Risk factors for delayed recovery following a concussion

Preexisting conditions	Past medical history	Psychosocial history	Injury factors	Medication use	Family history
Learning difficulties (especially in early school years)	Migraine and exercise-induced headache	Previous stressful life events	Severity of acute symptoms	Analgesic use and/or overuse	Migraines, hemiplegic migraine
Attention-deficit disorder	Previous concussions especially with delayed recovery	Recent stressors and the child's reactions to these (i.e., conflicts)	Mechanism (i.e., high energy)	Alternative therapies	Attention deficits; learning disorder in first-degree family may support preexisting diagnosis in child
Anxiety		Loss of a family member/friend or pet	Assault (associated with delayed recovery)	Use of marijuana or illicit substances	Anxiety
Depression		Change of school	Litigation		Depression

fatigued (79%), more emotional than usual (60%), and irritable (58%) and have frequent headaches (58%). The prevalence of PCS at 3 months post-injury is around 10–25%. Approximately 2% of all children with mTBI will remain symptomatic up to 1 year or longer [31, 43, 51]. Often, the persistence of these symptoms can result in delayed return to school, impaired academic performance, depressed mood, social isolation, and lower quality of life.

The International Classification of Diseases (tenth edition) and the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) have different diagnostic criteria for PCS. Neither has been validated in children, and both are usually modified to suit clinical practice. We recently proposed pediatric diagnostic criteria for PCS following an mTBI:

(a) A history of mTBI with an onset of symptoms or signs within 72 hours of the injury.
(b) The presence of at least three of the following symptoms: headache, dizziness, fatigue, irritability, insomnia, difficulty concentrating, memory problems, emotional labiality, and mood disturbances.
(c) Symptoms have been present for at least 4 weeks post-injury.
(d) Symptoms are not better explained by another disorder.

Several preexisting medical conditions and post-injury symptoms are associated with poor outcomes following mTBI. Common risk factors for PCS are shown in Table 3 and include age, injury severity, and severity of baseline symptoms. The "Clinical Risk Score for Persistent Postconcussion Symptoms" is helpful for predicting short-term outcomes, but the ability to predict which child/adolescent will continue to have symptoms lasting 3 months or longer is difficult [40]. Overtime, premorbid sociological and psychological factors, as well as the presence of medicolegal issues, increasingly contribute to outcome – eventually becoming the predominant factors. For these reasons, the clinician should pay particular attention to risk factors for poor recovery as well as PCS mimics [50]. Clinicians should also beware of the tendency for patients to attribute problems to an mTBI when it could be due to a preexisting problem or condition (Table 3).

PCS often requires a multifaceted approach, assessing current symptoms (physical, emotional, and sleep) and cognition as well as vestibular and oculomotor function. Clinical evidence to support other diagnoses should be investigated including cervicogenic headache (neck pain, facet joint pain, occipital neuralgia, decreased range of movement of the neck, and muscle tenderness), vestibular dysfunction

(suggestive findings of head impulse test, Dix-Hallpike maneuver, dynamic visual acuity testing), temporomandibular joint dysfunction, convergence insufficiency, and/or asymmetrical refractive errors.

Management of PCS

The management of PCS differs from acute and subacute recovery phases following an mTBI. Often, a referral to a multidisciplinary specialized rehabilitation center is warranted with the focus to improve general functioning, increase activities of daily life and return the child back to school, and provide early reassurance. This is achieved by supporting the child/adolescent in their daily and routine environments. Such support is generated by reassurance and encouragement from all parties involved in their care, as well as returning the child/adolescent to school and other activities via a graduated fashion. Participation in school and social activities should be encouraged while this occurs. With gaining a clear understanding of the various factors contributing to symptom persistence, a clinician should target their advice toward one or two of the most problematic symptoms, as the other symptoms will often improve with this line of targeted management strategies. Unless cognitive difficulties are suspected, sleep, headaches, and mood disturbances (such as anxiety or depression) should be addressed first, as these can all influence cognitive performance. Persistence of neuropsychological impairment after mTBI is still debated [52].

Posttraumatic Headaches

Headaches that are related to a concussion usually begin within 7 days of the concussion. A pre-injury history of headache (such as migraine) may or may not be present. Preexisting headaches often become worse after a concussion. Further, headaches with different characteristics from the pre-injury headaches can also occur. The overarching approach to headaches after a concussion is to characterize the headache type and triggers and endorse the practice of good headache hygiene behavior. This includes regular sleep habits, healthy meals, hydration, caffeine limitation, and the management of stress. The medical management of posttraumatic headaches is determined by pre-injury headache diagnosis, characteristics of the new headaches, severity of the headaches, length of the headache disorder, and management of comorbidities, especially anxiety and mood changes.

The majority of acute posttraumatic headaches resolve by 4 weeks with the use of good headache hygiene practices and treating the associated pain with ibuprofen, naproxen, or acetaminophen. In children, it is essential to ensure that analgesics are used with sufficient and correct dosing and with attention to daily maximums. It is useful to consider optimizing the medical management of any pre-injury headaches (especially migraines). After 2–4 weeks, analgesics should be limited to three times or less per week to avoid medication overuse-associated headaches (rebound phenomenon). It is important to note that triptans have not been evaluated, and we do not recommend them in the treatment of acute posttraumatic headache in children.

Dizziness and Balance Problems

Dizziness is a commonly reported symptom following concussion and has been reported to predict a longer recovery. What children mean by dizziness is variable. For some, it may mean lightheadedness, nausea, spinning, dysequilibrium, or even blurred vision. Therefore, it is important to determine what is meant by dizziness and treat as appropriate. Complaints of orthostatic symptoms like lightheadedness or dizziness may respond to increased fluid and salt intake, whereas vertigo that is exacerbated by a change in head position is commonly seen in benign paroxysmal vertigo and often responds to a repositioning procedure, such as the Epley maneuver.

Balance alterations may occur in a significant number of children, but often will get better

without specific intervention over the first 10 days. It is not recommended to avoid movement or mild aerobic activity because of dizziness or balance problems. Dizziness associated with neck pain and/or headache may respond to treatment with specialized physiotherapy [53, 54].

Children/adolescents with persistent complaints of vertigo, balance problems, or visual problems should be referred onto a specialist. Some management strategies that can be employed include specialized physiotherapy for peripheral vestibular dysfunction [55] and/or prophylactic agents for migraines in cases to treat migrainous vertigo [56].

Visual Symptoms

Concussion/mTBI-related visual complaints include blurred/double vision, eye fatigue, the appearance of words moving on the page, loss of place when reading, and difficulty sustaining attention on a visual task. Identification of visual problems is important because approximately 50% of the brain's circuits are dedicated to vision [57]. With the visual demands of children/adolescents engaged in full-time school (due to widespread use of electronic interfaces), treat any visual acuity deficits with spectacles. Specific issues like convergence insufficiency may respond to home exercise programs often known as pencil push-ups. Specific school-based accommodations are usually not required for typically recovering children. In some children, short-term accommodations, such as frequent visual breaks and preprinted notes and material, may be useful. Accommodations, such as oral teaching, audio books, or large-font printed material (vs. small-font electronically displayed material), are not required unless recommended by an ophthalmologist, pediatrician, or neurologist [58]. Occasionally, a referral to a concussion specialist or eye care professional is needed for a comprehensive visual and oculomotor evaluation. Oculomotor neurorehabilitation for convergence insufficiency and persistent reading dysfunction [59] may be useful to treat preexisting problems but should not be recommended routinely. The value of oculomotor retraining (including use of prisms) in concussion has not been proven and is not recommended for routine use except under guidance from ophthalmology or neurology.

Mood Symptoms

Mood changes and anxiety can be common during recovery from an mTBI. As mentioned above, many children worry about failing at school, not being active, or feeling left out. These feelings may make symptoms worse (especially headaches and attention and concentration difficulty) and prolong recovery. Social isolation has been identified as a risk factor of poor recovery and should be avoided during the recovery process. Hence, 2 to 3 days post-injury, the child/adolescent should return to half-days of schooling (ideally the morning half) and stay over the lunch hour. They can participate in schoolwork during this time, and interaction with friends and peers should be encouraged. Best practice guidelines support the importance of providing social support to improve quality of life and reduce effects of stressors on a child/adolescent's health. Such supports include as follows:

- Counseling services
- Emotional guidance (empathy, love, trust, and caring) by caregivers (from parents/guardians, teachers, coaches, friends)
- Informational guidance and appraisal (constructive feedback and positive affirmations)
- Provision of tangible aids/services directly assisting needs of the child/adolescent

Cognitive behavioral therapy has been demonstrated to be of value in PCS [6, 60]. Clinicians should be aware of avoidant behaviors; these are often associated with anxiety and should not be encouraged. If suspected, it is helpful to have a psychologist or counselor become involved. If the child/adolescent was seeing a specialist/healthcare provider for mood- and anxiety-related symptoms pre-injury, encourage a follow-up visit with them and encourage the use of psychotherapy to aid recovery [45–47, 61].

Neck Pain

Neck pain is a common symptom following concussion. The cervical spine may be injured secondary to trauma and is widely cited as a source of neck pain and headache in the whiplash literature. A combination of manual therapy and exercise has been shown to be more effective than passive modalities for individuals with neck pain (53).

Summary

Concussion is a common problem in children, and repeated injuries often occur especially in sport. Although rapid resolution of symptoms is the norm, a significant proportion of children take several months to improve. The mainstay of management is early recognition and cessation of play. Depending on the level of symptom acuity, children should be assessed by the ED physician or the family doctor. After a short period of rest, children should gradually return to school and then physical activities. For most children, this is completed over 2–4 weeks following the injury. However, other children have significant problems with PCS, headaches, and mood disturbances which require careful evaluation. Therapies can then be targeted to the most problematic symptom or are applied as part of a multidisciplinary program. There remains a great need for the development of treatments targeted to children with PCS and other post-concussion disorders.

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Chronic Traumatic Encephalopathy

Diego Iacono and Daniel P. Perl

Traumatic Brain Injury (TBI)

Trauma to the head sufficient enough to affect the brain may cause a diversified series of transient and permanent neurological damage that have been a constant feature of humans and human-related activities [1–3]. Brain damage caused by a traumatic event is termed traumatic brain injury (TBI). Clinical definitions, classifications, staging systems, pharmacological and non-pharmacological treatments, and neuro-rehabilitation approaches for TBI have been revised multiple times over the last few decades [4–8]. Currently, one of the most accepted (and practical) definitions of TBI is "a form of acquired brain injury that occurs when a sudden trauma causes damage to the brain. TBI can result when the head suddenly and violently hits an object, or when an object pierces the skull and enters brain tissue. Symptoms of a TBI can be mild, moderate, or severe, depending on the extent of the damage to the brain. A person with a mild TBI may remain conscious or may experience a loss of consciousness for a few seconds or minutes. Other symptoms of mild TBI include headache, confusion, lightheadedness, dizziness, blurred vision or tired eyes, ringing in the ears, bad taste in the mouth, fatigue or lethargy, a change in sleep patterns, behavioral or mood changes, and trouble with memory, concentration, attention, or thinking. A person with a moderate or severe TBI may show these same symptoms, but may also have a headache that gets worse or does not go away, repeated vomiting or nausea, convulsions or seizures, an

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inability to awaken from sleep, dilation of one or both pupils of the eyes, slurred speech, weakness or numbness in the extremities, loss of coordination, and increased confusion, restlessness, or agitation" (http://www.ninds.nih.gov/disorders/tbi/tbi.htm).

Etiologically, TBI can be caused by different types of events (i.e., natural and nonnatural), involve different types of energies (i.e., mechanical and nonmechanical), various physical dynamics (i.e., impact and nonimpact), different temporal patterns (i.e., sTBI, rTBI), as well as immediate or delayed functional consequences (i.e., loss of consciousness, prolonged arousal disorders, reduced awareness, chronic headache, memory and anxiety disorders, seizures, etc.). Naturally occurring head accidents (i.e., cranial fractures, falls) and head trauma related to human activities (physical fighting, physical abuse, movement disorders, etc.) [9, 10], inventions, or tools (i.e., motor vehicles, contact sports, weapons, explosions, occupational tools, etc.) [11] continue to represent a major global public health concern [12]. This concern is mainly due to the high rate of mortality and significant morbidity that is particularly associated with moderate and severe TBI in both civilian and military populations [13–16].

The first attempts to define the specific effects of TBI in terms of possible medical (biological) consequences started during the late nineteenth century [17, 18]; however, it was not until the first two decades of the twentieth century that a more systematic study of TBI actually began [19–22].

This chapter succinctly summarizes the current state of knowledge of the neuropathologic consequences associated with TBI, with a particular focus on the neuropathologic consequences of rTBI and blast-TBI, which are, respectively, the two specific types of TBI that most frequently involve younger civilians (particularly athletes who engage in contact sports) and active duty military personnel.

Historical Background

Chronic traumatic encephalopathy (CTE) is the current neuropathologic terminology used to define the ensemble of microscopic lesions observed in the brains of persons with a history of rTBI. The term CTE was introduced in the English-language medical literature by Macdonald Critchley in 1957 [23], who aimed to systematically describe the long-term clinical outcomes of eleven men who practiced professional-level boxing leading to a "punch-drunk" state. In 1928, the characteristic neuropsychiatric syndrome that can affect some professional boxers, which were "in the game long enough," was indeed described by a medical examiner from Newark, New Jersey, Harrison Stanford Martland, who coined the term "punch-drunk" syndrome [24]. In 1937, J.A. Millspaugh, a lieutenant of the US Navy Medical Corps, introduced the term "dementia pugilistica" to describe a clinical syndrome characterized by a series of diverse chronic cognitive and motor deficits he had observed in several professional boxers [25]. The term "dementia pugilistica" was actually introduced for the first time, in the German-language medical literature, by Jokl and Guttmann [26]. However, in 1927 Italian researchers already described a condition related to the possible neuropsychiatric consequences of rTBI, which they termed "post-concussion neurosis-traumatic encephalitis" [22].

Except from very sporadic descriptions of brain lesions associated with peculiar types of TBI (e.g., explosive-related TBI) published at the beginning of the nineteenth century [27] and some reports written during World War II [28], which have been scarcely considered for a long period of time, it is only starting in the 1950s that more systematic analyses and a common medical language began to be used to describe brain lesions possibly associated with TBI and specifically with rTBI. In fact, the initial cases of TBI analyzed by Corsellis and coauthors in 1959 [29] were indeed rTBI cases, that is, autopsy-brains of former professional boxers. After Corsellis' seminal publication, autopsy-brains from other "natural models" of rTBI, essentially persons that practiced contact sports other than boxing [30, 31], began to appear. Altogether, these studies contributed to a closer identification and description of possible brain lesions characteristically observable in rTBI individuals in comparison to brains of those either with a history of sTBI or without a history of TBI [32].

During the last century, brain lesions identified as typical of rTBI have been termed in different ways such as "traumatic progressive encephalopathy," "dementia pugilistica," "boxers' encephalopathy," and others. Currently, however, CTE has been the term more globally accepted to refer to the neuropathologic consequences of rTBI. CTE was systematically described and formally defined for the first time in 2016 [33]. However, in our opinion, while the term CTE is now commonly used, it will likely be modified further in the near future. In fact, the term "chronic" ("condition persisting for a long time or constantly recurring" in an individual) suggests that the brain pathology associated with rTBI could disappear after a long time, or be a recurring phenomenon, which is obviously not the case (rTBI-related brain lesions cannot disappear or recur but only progressively accumulate); and the term "encephalopathy" is a broader term commonly used in medicine to define a cluster of signs and symptoms associated with one or more possible conditions (usually progressive but reversible conditions, and more often metabolic, such as hepatic or uremic encephalopathy) until a specific cause is recognized and after that allowing for the possibility that *a syndrome* could be precisely defined as *a disease* (an illness with an identified cause and natural history). By consequence, if CTE will be demonstrated to be a specific brain disease (pathognomonic pathology for typical clinical signs and symptoms with known causes), the term "encephalopathy" should be replaced by the term "disease." As a result, a more correct terminology to define the clinico-neuropathologic correlates of rTBI (or TBI in general) could or should be "traumatic brain disease" (TBD) or "post-traumatic tauopathy."

CTE currently remains a postmortem diagnosis defined by the pathognomonic presence of hyperphosphorylated tau (pTau)-immunoreactive positive neurofibrillary tangles (pTau-NFT), pTau-neurites, and pTau-dot-like lesions localized in the more superficial neocortical layers (II/III) at the depths of the cerebral sulci, with a peculiar topographic predilection for perivascular areas of intracortical small vessels (Figs. 1a, b, 2a–h, and 3a–f). Moreover, pTau-positive aggregates can be present not only in neurons but also in astrocytes and other types of cells (e.g., microglia) and cellular processes (e.g., synaptic clefts). However, it is important here to recall that pTau aggregations are not the only type of pathologic aggregations detectable in rTBI brains. Extracellular deposition of β-amyloid, phosphorylated transactive response (TAR) DNA-binding protein 43 kDA (pTDP43) intraneuronal inclusions, alpha-synuclein (α-syn)-positive lesions (Lewy bodies (LB) and Lewy neurites (LN)), and neuroinflammatory and immune reactive cells are all also detectable in various amounts and in different cellular and subcellular localizations, at various levels of activation, and with peculiar histological distributions in rTBI cases.

a

American Football
Boxing
Martial Arts
Rugby
Soccer
"Wife shell-shock"
Autism (head-banging)
Others?

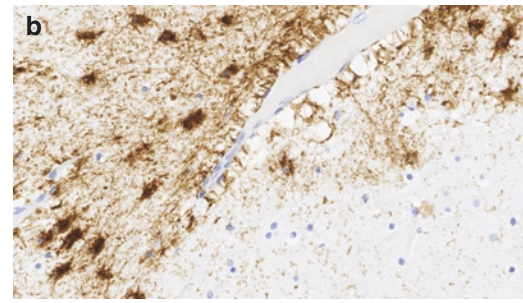

Fig. 1 (**a**, **b**) Contact sports and human activities associated with a diagnosis of chronic traumatic Encephalopathy. (**a**) A summary of the various contact sports and human activities that have been associated with a diagnosis of CTE. (**b**) CTE pathology shows a microscopic image of phosphorylated-tau-positive neurofibrillary tangles in the depths of a cortical sulcus. Immunohistochemistry was performed using AT8 antibody

The "Renaissance" of CTE

An explosion of studies aiming to investigate in further detail the TBI-related pathology using human and animal tissues has undeniably occurred during the last few decades [34]. The current "Renaissance" of CTE and the corresponding

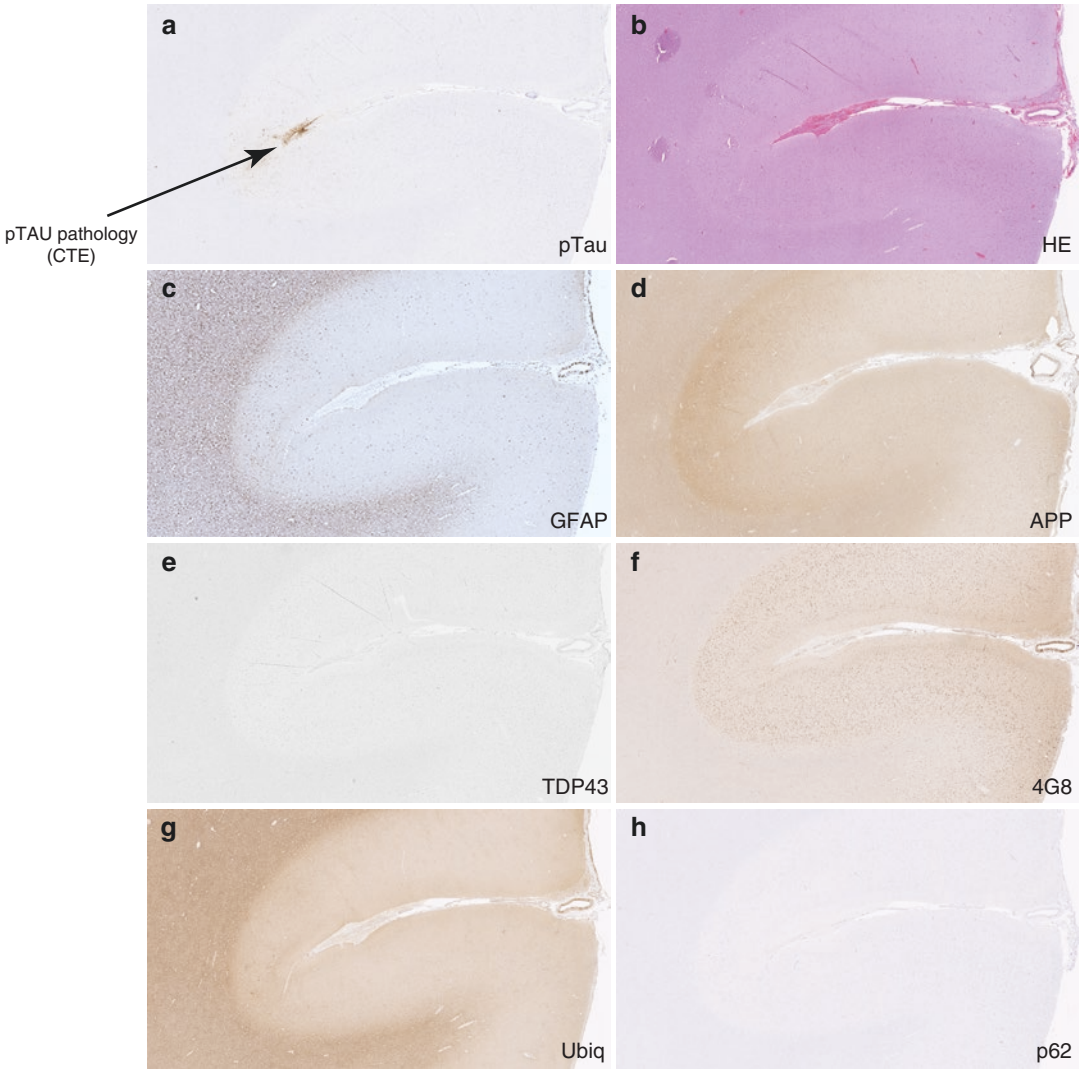

Fig. 2 (**a**–**h**) Synoptic immunohistochemistry views of the same neocortical region from a brain of a subject diagnosed with chronic traumatic encephalopathy (CTE). Deep in the cortical sulcus, it is possible to identify lesions positive for hyperphosphorylated-tau (pTau-neurofibrillary tangles; pTau-NFT). The antibody used for pTau detection was AT8 (a mouse monoclonal antibody recognizing phosphorylated-tau protein at Ser202 and Thr205 amino acid). Series of consecutive sections of the same cortical area do not show any lesion positive for GFAP, pTDP43, ubiquitin, or p62 protein. To note, pTau lesions (pTau-NFT) are invisible at the microscopic inspection when analyzed with H&E stain

increasing number of investigators involved in CTE research is mainly due to the evidence that CTE is observed not only in contact sports athletes – per se an already important social, educational, and economical issue – but also in subjects with a history of rTBI linked to nonprofessional, recreational, or occupational activities. For example, CTE has additionally been recognized in autistic subjects (i.e., head-banging) [35], in a case of "punch-drunk wife" [36], and in a circus "dwarf clown" [37]. In addition, a very special situation is represented by the possible presence of isolated CTE lesions, and potentially related long-term neurodegenerative effects, in the brains of military personnel exposed to blast-TBIs [38].

After the initial studies from Corsellis' and collaborators [29, 39], who was indeed the first author to describe neuropathologic changes in a larger series of boxing players' brains after Martland's original description, a series of more recent neuro-

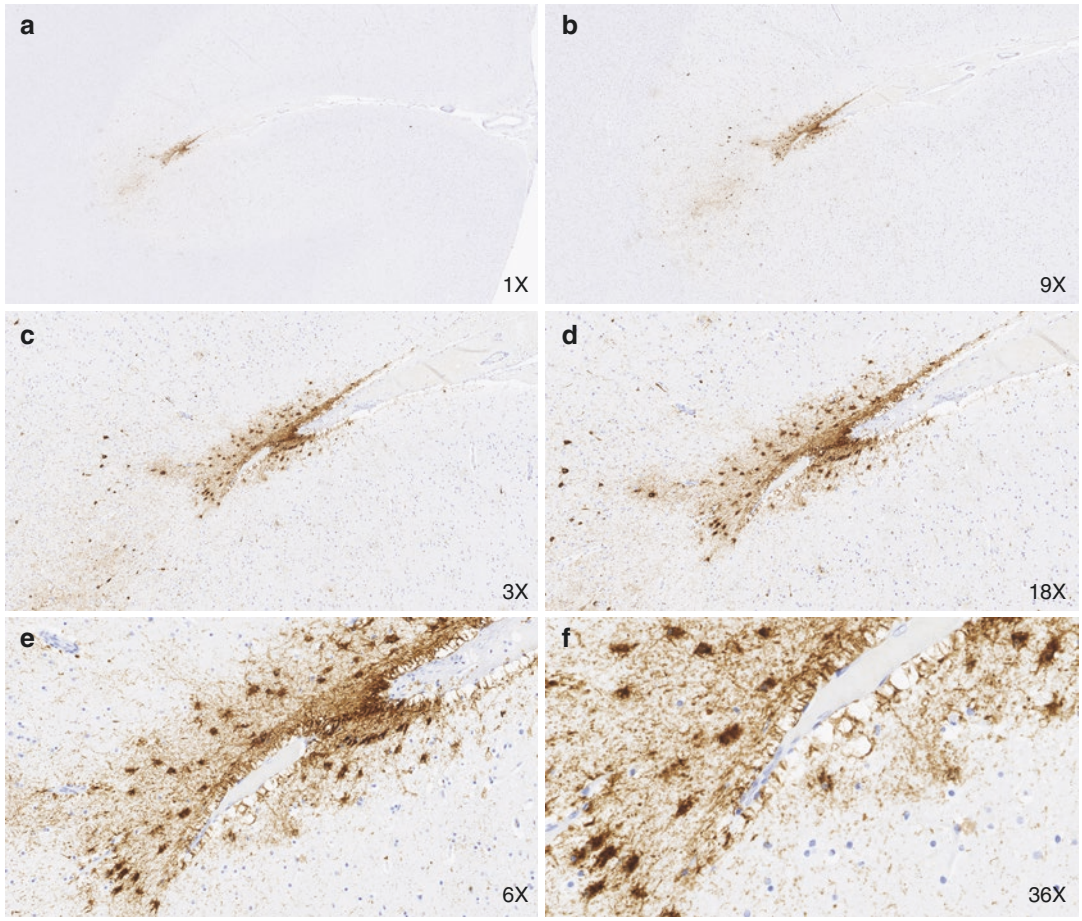

Fig. 3 (**a**–**f**) pTau pathology in CTE. Progressive magnification (1× (A), 3× (B), 6× (C), 9× (D), 18× (E), 36× (F)) of the same neocortical area showing sulcal accumulation of pTau lesions (pTau neurofibrillary tangles, neurites, and dot-like lesions). The brain of a subject with a postmortem diagnosis of CTE and a documented history of repetitive TBI (45-year-old man who practiced boxing and wrestling)

pathologic observations were reported by Roberts and coauthors in 1990 [40] and by Omalu and coauthors in 2005 [41]. Omalu and collaborators were the first authors to describe CTE in a North American football player. After Omalu's seminal report in 2005 [41], an increased level of awareness about CTE and its related possible long-term neurodegenerative/neuropsychiatric consequences has been recorded. This increased public and scientific awareness about CTE returned in 2016 in a more extensive investigation of relatively large numbers of cases mostly related to participation in professional American football [42–44]. It is thanks to these latter efforts that CTE gained major scientific dignity in consideration of the enormous social, educational, and political issues that a future confirmation of a significant association among rTBI, CTE, and long-term neurodegenerative consequences could imply in terms of major changes for civilian practices, military activities, and preventive countermeasures.

CTE: Neuropathology of Repetitive TBI (rTBI)

Macroscopy

For the neuropathologist, the external examination of an autopsy-brain from a subject with a history of rTBI represents the opportunity to observe and verify the presence of specific macroscopic cerebral alterations in that specific rTBI brain/subject and by consequence progressively

accumulate observations on possible common features of rTBI macroscopic appearance. These macroscopic observations are essential to guide other investigators (e.g., not only neuropathologists but also neuroradiologists) to recognize and differentiate the typical macroscopic abnormalities associated with a history of rTBI from other conditions (e.g., malformations). These features are also extremely useful to hypothesize pathophysiologic mechanisms triggered by rTBI events. Furthermore, the characteristic macroscopic patterns of alterations associated with rTBI detected by in vivo neuroimaging analyses (e.g., MRI, PET) can be confirmed as well. Moreover, the acquisition of macroscopic rTBI-related abnormalities "in vivo" and their comparison with "ex vivo" analyses followed by the definitive neuropathologic assessment on the same brain represent an unprecedented opportunity to further investigate longitudinal clinicopathologic aspects that were not imaginable a few years ago [45, 46].

The typical macroscopic changes observed in an rTBI brain are:

1. Reduction of the brain weight, which often corresponds to a mild-to-moderate degree of diffuse brain atrophy, including both white and gray matter, which is clearly unusual for the age of the subject [47]
2. Possible cerebellar atrophy [48]
3. Mild-to-moderate enlargement of the lateral ventricles, especially of the frontal and temporal horns and third ventricle [49]
4. Cavum septum pellucidum (with or without fenestrations]) [50]
5. Global and unusual atrophy of subcortical structures, such as the corpus callosum (especially its caudal aspect), thalamus, subthalamus, hypothalamus, mammillary bodies, midbrain, pons, and medulla [51]

Microscopy

CTE and Tau

Formation and accumulation of pTau protein aggregates in the form of pre-tangles, tangles, threadlike, and dot-like lesions in neurons and astrocytes, which tend to be localized around the perivascular areas of small intracortical vessels in the depths of cortical sulci (gray matter), are currently considered pathognomonic microscopic feature of CTE [33]. The pathognomonic aspect of pTau pathology in CTE is actually due to its topographic distribution more than its nature per se (Fig. 1a, b). In fact, pTau intracortical sulcal perivascular lesions are mainly, if not exclusively, observed in the brains of persons with a history of rTBI (in particular, persons with a history of engaging for many years in contact sports) in comparison to the brains of persons without a history of rTBI. This typical topographic distribution of pTau lesions in CTE is indeed quite different from the anatomical and histological distribution observed, for example, in other pTau-associated brain diseases, such as Alzheimer's disease (AD) [52], progressive supranuclear palsy (PSP) [53], or cognitively intact older subjects [54]. Specifically, pTau-positive lesions (i.e., pTau-NFTs) in CTE cases are typically localized in layers II and III of the neocortex, while in AD they are mainly localized in the deeper layers of the neocortex [55–57]. Another topographic difference about pTau lesions between CTE and AD pathology is its prevalence in the CA2 sector of the hippocampus and the mammillary bodies in CTE cases. These areas of involvement are rarely observed in AD cases, even in the most advanced cases. These peculiar aspects of the pTau pathology distribution in CTE/rTBI autopsy cases and the lack of extracellular β-amyloid accumulation in many cases is one of the principal reasons that CTE is considered to be a primary tauopathy [43]. Although pTau lesions are certainly one of the main features of CTE, and one on which the ongoing CTE staging system relies, it is certainly not impossible that other types of misfolded proteins' formation and pathologic accumulation can be, at various pathogenetic levels and timing, involved in the initial pathogenetic stages of CTE, that is, rTBI-related pathology or TBI-related pathology more in general [58–61]. A series of cytoskeletal proteins apart from tau, a normally present soluble microtubule-associated protein-stabilizing neuronal cytoskeleton which serves to maintain the neuro-

nal cytoskeletal stability [62], can be potentially involved with and react to various types of energies and distortional phenomena involved in TBI (e.g., neurofilament, tubulin, actin, etc.). Each of these affected proteins (e.g., neurofilament light protein [63]) could create an impaired or dysfunctional cellular environment not directly or primarily linked to tau abnormalities [64]. By consequence, the specific dynamics (i.e., acceleration-deceleration phenomena, rotational forces, penetrating injury, blast), temporal patterns (single, repetitive, single + repetitive), and intensity (light, mild, severe TBI) of each specific type of brain trauma can, theoretically, induce several types of cellular disarrangement, which may not be exclusively, or initially, associated with the accumulation of pTau in the cortical sulci around perivascular areas. Even more, though, the peculiar distribution of pTau in CTE cases (i.e., rTBI) in comparison to non-CTE cases (i.e., sTBI) could acquire a fundamental relevance since it could reveal some peculiar pathophysiologic aspects of CTE such as the specific site of tau phosphorylation as related to a specific cortical layer. The pathogenetic relevance of the peculiar anatomo-histologic distribution of pTau in CTE seems in fact to be reinforced by the fact that no clear-cut biochemical differences have been found between CTE and non-CTE tau pathology in terms of tau isoforms [65], phosphorylation process, and antibodies used to detect it (e.g., AT8, CP13, and PHF-1, which are the most common antibodies used to detect pTau pathology in human brain tissues, show comparable results in CTE cases). These considerations further suggest that the pTau localization in CTE is intrinsically linked to the actual physical forces and dynamics involved in rTBI. The peculiar topographic and histologic distribution of pTau pathology in human CTE, unfortunately, represents one of the main elements of difficulty for the creation of animal models to possibly recapitulate CTE in lab model. Most of the animals used in the labs, such as small rodents, cannot actually reproduce the peculiar histological features of CTE, as currently defined in humans at least [33], due to the fact that brain gyrification (formation of cortical gyri and sulci during neurodevelopment) is not present in those animals. It is also important to recognize that other factors such as age, sex, genotype, epigenetic changes, as well as environmental and behavioral risk factors, can likely either positively or negatively modulate the formation/accumulation of pTau in CTE. Furthermore, some of those risk factors could hinder or facilitate the anatomical propagation and progression of CTE (or of some other specific misfolded protein as well) and its long-term neurodegenerative spreading effects [66]. A staging system of CTE has been proposed based on the specific regional anatomical distribution of pTau found at autopsy [67]. Although useful as a guide for future studies on the possible progression of CTE and quantitative correlation between CTE anatomical spreading and rTBI duration/intensity, there are no currently available studies to validate the proposed CTE staging system as a clinicopathological tool [68]. Currently, CTE is not yet a disease (i.e., a well-defined criteria-based clinical entity with a known cause or causes) but rather the detailed description of pathologic correlates possibly associated with different clusters of symptoms and signs linked to a history of rTBI in the context of very specific human activities (i.e., contact sports).

CTE and β-Amyloid

As for the tau protein, also other intracytoplasmic proteins and subcellular components can be affected by biomechanical forces [69]. At a microscopic level, and before a more detailed definition of CTE was proposed, diffuse axonal injury (DAI) was considered the only specific and pathognomonic sign of TBI, especially of sTBI [70–73]. DAI has been considered for years to represent the characteristic postmortem evidence for TBI, and for this reason, it is frequently used in forensic neuropathology cases [74]. DAI, essentially, signifies abnormal or completely interrupted axonal transport and can be easily detected by the presence of axonal spheroids on routine morphologic stains or by immunohistochemistry protocols using antibodies against the β-amyloid precursor protein (βAPP) [75] (Fig. 4d). DAI is a very early sign of axonal damage, being detectable even a few

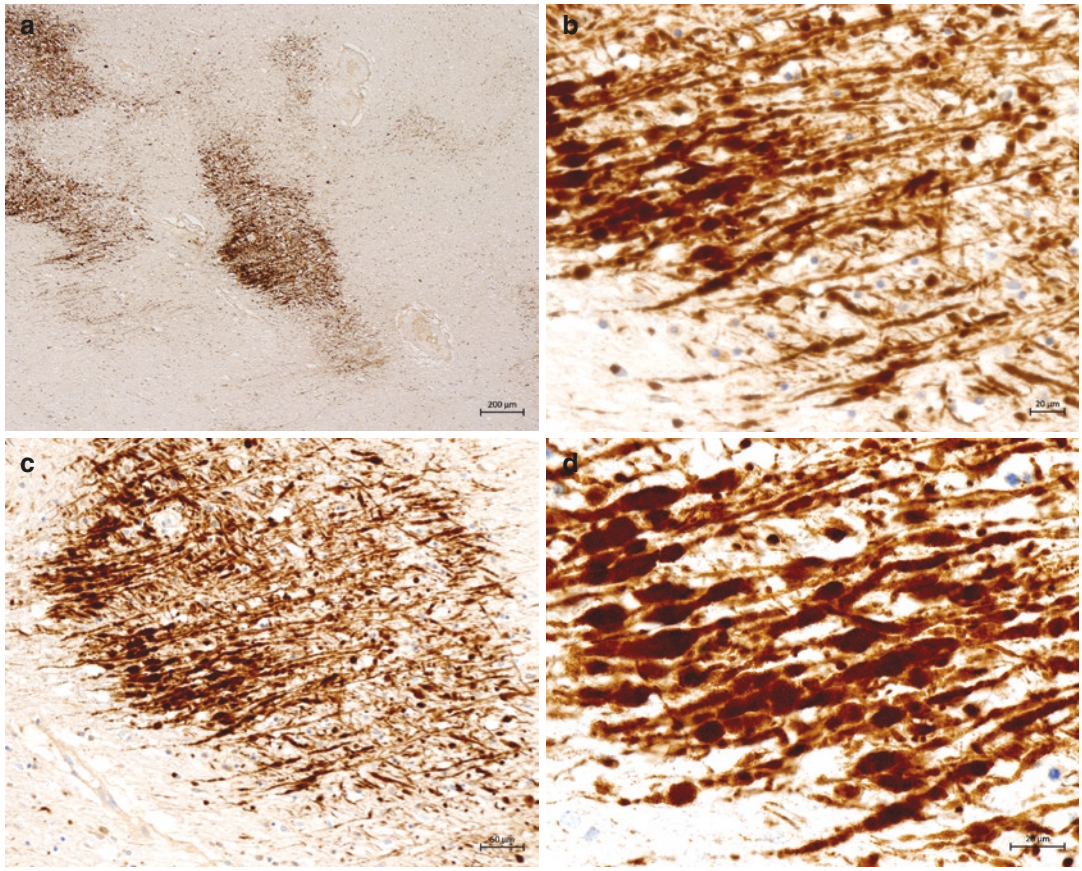

Fig. 4 (**a**–**d**) Corpus callosum of a person with a history of single TBI (sTBI). Immunohistochemistry with APP identifies multiple sites of axonal injury (brown fibers) and axonal swallowing (elliptical/spherical brown elements better visible at higher magnification as in **d**)

hours after the TBI [76, 77]. Furthermore, DAI is considered a sign of acute axonal damage in sTBI and is not frequently observed in CTE (rTBI) cases. This could be explained by the fact that CTE has been often analyzed in younger subjects where neuronal-clearance systems are still efficient enough to provide restoration of the normal axonal transport and βAPP clearance [78]. βAPP, however, is the precursor of β-amyloid protein, which is one of the main constituents of the neuritic senile plaques found in AD [79]. Diffuse amyloid plaques (indistinguishable from the ones found in AD and more commonly in elderly individuals with intact cognition) have been detected in perilesional areas of both sTBI and rTBI brains [70–73]. The presence of β-amyloid plaques and insoluble extracellular β-amyloid deposition in TBI cases could potentially represent a prodromal sign for the activation of the amyloid cascade [80, 81], which could theoretically induce long-term neurodegenerative effects culminating in alterations to synaptic function and loss and consequentially in the loss of neurons and their related functions. Nevertheless, it is not known yet if β-amyloid plaques in rTBI (CTE) cases are simply correlated with the age of the person at the time of the trauma, aging being per se a risk factor for the extraneuronal accumulation of β-amyloid [82] or rather, if some other specific genetic (including allele APOE ε4, the major genetic risk factor associated with increased accumulation of β-amyloid and dementia risk) [83] or if some still unknown environmental risk factors could

influence β-amyloid plaque formation as a direct consequence of TBI [84–87]. Increased plasma levels of various molecules (e.g., β-amyloid, tau, and glial fibrillary acidic protein (GFAP)), have been detected after acute TBI (sTBI) [88]. Furthermore, it is not known if there is a person-based threshold (e.g., a certain number of the same type of TBI) after which a repeated acute increase of plasmatic proteins can trigger more stable phenomena of intra- or extracellular misfolded protein accumulation. It is also important to consider that some of the biomarkers associated with acute TBI can potentially have different and even opposite mechanisms (degenerative vs. reparative processes) in terms of brain response, and thus denote different prognostic and clinical outcomes [89].

CTE and TDP43

The transactive response (TAR) DNA-binding protein 43 (TDP43) is a 43-KDa nuclear protein expressed in different types of tissues throughout the human body [90]. Intraneuronal (intranuclear) inclusions with positive immunoreactivity to phosphorylated-TDP43 (pTDP43) have been associated with cases of frontotemporal dementia (FTD) [91]. However, positivity to TDP43 (non-phosphorylated and probably not pathologic) has also been observed in cognitively healthy older persons as well as across all CTE stages [92]. In the later stages of CTE, TDP43-positive lesions (non-pTDP43) can be observed in the same neurons with pTau-positive lesions [93]. Nevertheless, to the best of our knowledge, intranuclear inclusions positive for pTDP43, which is the pathologic form of TDP43, have not been reported in CTE cases [94]. The possible TBI-induced accumulation of pTDP43 intracellular inclusions in CTE (rTBI) cases will need to be confirmed in future clinicopathologic rTBI studies. The relationship between CTE and pTDP43 lesions could potentially acquire an important pathogenetic relevance since pTDP43 intraneuronal inclusions have been reported in cases of frontotemporal dementia/amyotrophic lateral sclerosis (FTD/ALS) [95] since some ALS cases have been epidemiologically associated with rTBI [96].

CTE and Alpha-Synuclein

Alpha-synuclein (α-syn), a normally expressed presynaptic protein whose function is still unknown, has been demonstrated to be the main molecular constituent of Lewy bodies (LB) and Lewy neurites (LN) [97]. LBs and LNs are intracellular lesions initially observed in nigral and non-nigral neurons of patients with Lewy body disease, specifically Parkinson's disease (PD) and Dementia with Lewy bodies (DLB) [98]. In addition to LBs and LNs, PD patients are typically characterized by neuronal loss of pigmented neurons in the *pars compacta* of the substantia nigra (SNpc). However, the possibility of a direct correlation between nigral neuronal loss in the absence of Lewy pathology and nigral neuronal loss in the absence of LB pathology (but positivity for tau-NFTs) has been observed in studies of retired professional boxers [99]. In support of this latter hypothesis, it is observed that no direct correlation between LB pathology burden and nigral neuronal loss (dopaminergic-pigmented neurons) is available during the initial stages of PD progression. It has been calculated that at least 50% or more of nigral neurons need to be lost in order to originate the initial clinical appearance of extrapyramidal manifestations and that this neuronal loss does not correlate with the LB pathology load [100]. To date, there are no quantitative studies (e.g., using unbiased stereology methods) that have analyzed in human brains the possible direct correlations between the number and type of TBIs and nigral neuronal loss. However, animal model experiments suggest that α-syn could indeed participate in initiating pathogenetic mechanisms linking TBI and PD [101, 102]. Intriguingly, a large retrospective epidemiological study showed that a single TBI (with loss of consciousness, LOC) is associated with an increased risk for parkinsonism rather than with dementia and AD pathology [103]. These data seem to open new perspectives and pathogenetic hypotheses on the long-term neurodegenerative effects associated with, or induced by, TBI with specific possible effects as related to the period of life during which the TBI occurred.

CTE and Neuroinflammation

Both sTBI and rTBI induce a series of complex sequences of molecular and cellular events promoting the activation of quiescent resident microglia, astrocytes, blood-brain barrier (BBB) permeability changes, and recruitment of cells from the peripheral (systemic) immune system (neutrophils followed by leucocytes and monocytes "attracted" to the site of injury by specific chemokines). In addition to the neuroglia activation and peripheral immune cell recruitment, dendritic cells, T cells, natural killer cells, phenomena of angiogenesis, neurogenesis, de- and re-myelination, neurotransmission alterations, synaptic repair, and spine remodeling [104–107] also participate in the general CNS reaction toward a TBI, a CNS that is indeed attempting to restore the "status quo" existing prior to the TBI event.

The precise molecular and cellular profiling, timing, cumulative effects, thresholds, and ratios between pro- and anti-inflammatory pathways in rTBI cases (a cluster of multiple acute TBIs repeated with a periodic temporal pattern) have been investigated in humans only recently. Consequently, most of our knowledge on TBI and neuroinflammatory response derives from animal models, which still need confirmation in humans.

CTE and Neuroglia

Oligodendrocytes

Oligodendrocytes ("the cells with few branches") are components of the white matter (WM) and represent the most abundant type of nonneuronal cell of the CNS. In the past, these cells were almost exclusively considered as a type of supporting cell for the neuronal axons (being the only source of myelin in the CNS). However, oligodendrocytes have recently acquired major attention due to a series of investigations demonstrating their capacity to produce and regulate the actions of various neurotrophic factors, such as glial cell line-derived neurotropic factor (GDNF), brain-derived neurotropic factor (BDNF), and insulin-like growth factor-1 (IGF-1), during either neurodegenerative or neuroregenerative processes [108]. Due to their ability to form and maintain neuronal homeostasis and repair myelin sheaths (essential components for the proper functioning of neurons) [109], oligodendrocytes have gained a special relevance for TBI research since the severity of the axonal damage caused by different types of TBI frequently leads to DAI (see following paragraph). Oligodendrocytes are also involved in immediate and delayed neuroinflammatory responses [110, 111]. Oligodendrocytes seem to significantly participate in the balance between pro- and anti-inflammatory processes and are able to switch from the one to the other. The persistence of pro-inflammatory responses (possibly due to oligodendrocytes activation) is directly associated with persistence of neuronal/axonal damage in TBI and related clinical consequences [112].

Only recently the more detailed consequences and interactions between oligodendrocyte activation and TBI and how these glial cells can participate in the phenomena of repair and neural plasticity has begun to be elucidated [113]. Particularly intriguing is the possibility that oligodendrocytes can possess and modulate reparative functions by acting on their progenitors (commonly identified by the expression of NG2 chondroitin sulfate proteoglycan) [114]. Oligodendrocyte progenitors are immediately activated after brain injury, contribute to the formation of glial scars, and may inhibit subsequent neuroregeneration [115]. Studies focusing on the possible induction of oligodendrocyte progenitors in human tissues diagnosed with CTE have not appeared.

Myelin

The process of myelination is not only linked to functional aspects of neurons (myelin increases the speed of neural impulses) but also contributes to the formation of specific motor, cognitive, and behavioral functions [116]. Demyelinating diseases and neurodevelopmental defects can determine a wide spec-

trum of neuropsychiatric diseases [117]. In the context of CTE, the capacity to induce clearance of axonal debris and trigger reparative processes of myelination [118, 119] opens new and exciting perspectives. The possibility of pharmacologically manipulating the "oligo" component of CTE and so modify clinical outcomes associated with TBI, especially rTBI where the variable levels of axonal damage are probably one of the main causes of the subjacent clinical, neuroimaging, short- and long-term pathologic aspects of TBI, could offer a feasible and effective treatment for these disorders.

Astrocytes

Astrocytes, along with oligodendrocytes, belong to the so-called macroglia of the CNS in contrast to the "microglia" cells of the innate immune system that are largely distributed throughout the CNS. Apart from the "reactive" function and capacities to induce the classic phenomena of "astrogliosis" and "glial scarring" after an injury, astrocytes are becoming further recognized as essential cells activated during neurodevelopment and serving as the "homeostasis keepers" of the CNS. Astrocytes work so synergistically with neurons that it would be more accurate to define the "astro-neuronal unit," as the fundamental cellular system of the CNS [120, 121]. When reacting, astrocytes undergo morphological changes (e.g., cellular hypertrophy) that are clearly observable by optical microscopy using standard histologic stains (H&E, for example), which are expressions of a reacting protein synthesis status [122]. This reactive status corresponds to the increased production of proteins such as GFAP [123]. Although astrogliosis initially appears to be a non-specific cellular reaction and part of a generic neuroinflammatory response of the CNS to injury, animal studies show that astrocytes express specific cellular markers during different phases of the neuroinflammatory process and are actually part of reactive-reparative processes leading to reconstitution of normal neuronal function [124, 125]. Specific studies of differential astroglial pathways in human brains with a diagnosis of CTE have yet to be reported [126]. A special case is represented by blast-TBI (see blast-TBI paragraph).

Microglia

The principal type of cell of the innate immune system of CNS is the microglial cell. For a long time, microglial cells have been considered as the "macrophages" of the neural tissue; however, microglial cells represent a distinct class of cells capable of multiple functions [127–129]. Due to a peculiar and unique environment, the brain, as the rest of the CNS, is kept tightly regulated by the innate CNS-specific immune system that is functionally interconnected with the CNS-specific lymphatic drainage system [130]. Both CNS-specific innate immunity and lymphatic systems interact with the BBB [131] as well as a series of sophisticated cell-mediated molecular pathways to protect the brain from both infectious and sterile injuries. In general, microglial cells, the innate immune cells of the CNS (the "sentinel cells" for any type of injury affecting the CNS), serve as the "sensing system" for pathogens and other types of injury, and they are "trained" to maintain CNS survival while also triggering an adequate global immune response and inducing, among others, the activation of "local" (neural) and "external" (systemic) immune system cells [132, 133]. Most of what we currently know about the innate neuroimmune system and its specific responses to TBI (single or repetitive) has been observed in animal models [134]. Although these studies need confirmation in humans, it is reasonable that the molecular machinery involved in the innate neuroimmune system activation is quite similar across species, especially across mammals.

A good example of the molecular intricacy of the innate neuroimmune system participating in both infectious and noninfectious injury is represented by the activation of toll-like receptor 4 (TLR4), a protein belonging to the toll-like receptor family [135]. This receptor can be activated by pathogens (i.e., viruses, bacteria) as well as by TBI events or their consequences (i.e., cellular debris, necrotic cells). Intriguingly, the absence of TLR4 partially reduces some of the secondary inflammatory

effects (pro-inflammatory) that are induced by TBI [136–138]. Another type of receptor involved in TBI-induced reaction is the purinergic receptors [139]. ATP (adenosine triphosphate), for example, another recognized inducer of the neuroimmune system, can be detected by purinergic receptors on microglial and astrocytic projections directed toward the site of injury [140–143]. Although a microglial response is observed in CTE, there have been no reports on the specific interaction between microglial activation and the purinergic system on the sulcal NFTs (seen in CTE) in rTBI human brains.

Ependymal Cells

Ependymal cells represent another essential component of the neuroglia [144]. They are highly specialized types of epithelial cells which line the cerebral ventricles and central canal (spinal cord) and are tightly connected with blood vessels to form the choroid plexus [145]. The ependymal cells participate in the production and metabolism of cerebrospinal fluid and should be considered as one of the "vulnerable" types of cells in TBI, especially in rTBI events. Due to their anatomical location, these cells are at the forefront of the "sensing system" (the cerebrospinal fluid) that physically transfers and adsorbs most of the impacting energies during a TBI. Studies which focus on the role of ependymal cells in CTE are lacking; however, animal experiments have shown that the ciliary system (one of the specific histological features of the ependymal cells is the presence of cilia) is affected by TBI [146]. The potential role of the ependymal ciliary system to alter pro- and anti-inflammatory responses and reparative factors [147], or the possibility that specific molecular mediators can be spread throughout the CNS (cerebrospinal fluid signaling) and regulate a more generalized brain reaction in TBI, remains unknown.

CTE and Genetics

To date, no single gene mutation or genetic variant has been associated with a diagnosis of CTE. However, while the probability that a single genetic variation or mutation could be associated with the formation of CTE is low, genetic risk factors and epigenetic modifiers associated with the progression of rTBI clinical outcomes, and possibly CTE, have begun to be explored [148–150]. A now "classic" genetic factor associated with an increased risk of dementia and the accumulation of β-amyloid plaques, the ε4 allele of the APOE gene [151, 152], appears to be associated also to different long-term clinical outcomes in TBI [153–155]. The presence of β-amyloid pathology in a subset of CTE cases suggested a potential link between APOE and CTE and, more specifically, between APOE ε4 and rTBI [156, 157]. So far, though, there are no definitive data on a direct pathogenetic link between a specific gene (including APOE ε4) and CTE. The possible detrimental effect of APOE ε4 in TBI could be linked to associated biological factors, such as aging. APOE ε4 has been shown to have a detrimental effect on short- as well as long-term cognitive and behavioral outcomes in pediatric versus geriatric populations [158, 159]. Furthermore, other genes such as neuroglobin [160], protein phosphatase 3 catalytic subunit gamma (PPP3CC), catechol-O-methyltransferase (COMT), ankyrin repeat and kinase domain containing 1 (ANKK1) [161], and glutamate transporter [162] have been proposed to have modulatory effects on clinical consequences and outcomes primarily of single moderate-severe TBI. However, it is not known if these genes have a modulatory effect on CTE pathogenesis.

CTE and Single TBI

The aim of this chapter has been to give an overview on CTE, a pathologic diagnosis historically associated with rTBI. Although the description of neuropathologic lesions associated with sTBI is beyond the aims of this chapter, it is important to recall that CTE, as currently defined (NINDS criteria) [33], has never been observed in sTBI so far, at least in acute sTBI cases. Nonetheless, some aspects of CTE have been reported to be present in some sTBI cases sometime after (i.e., greater than 1 year) the injury [163].

In general, it appears that the types of proteins involved in the pathologic accumulation of intra- and extracellular lesions associated with both sTBI and rTBI are similar, if not identical. This notion reinforces the idea that it is indeed the modality or frequency of the trauma (including severity, temporal patterns, type of impacting energies, intervals between repetitive traumas, speed, and others) likely to have greater relevance on the formation of neuropathologic changes rather than, for example, a specific genetic predisposition associated with a higher risk of misfolded protein accumulations in the brain. Moreover, modalities and frequencies of TBI need also to consider the possible modulatory effects (either detrimental or beneficial) of biological and non-biological factors. These considerations altogether could well explain the constant pattern of anatomical localization (neocortical sulci) and histological similarities (perivascular tangles) observed across CTE cases (mostly American Football players) due to the relatively restricted types of trauma modalities (spatiotemporal dynamics). Finally, all previous considerations seems to suggest that it would be extremely useful to establish, at an international level, a more specific TBI medical terminology that serves to distinguish among sTBI, rTBI, and multiple TBI (i.e., combination of sTBI and rTBI).

CTE and Blast-TBI

Blast-TBI primarily related to exposure to improvised explosive devices (IEDs) represent a unique type of TBI that both civilian [164, 165] and military populations [166] have begun dealing with during the last few decades. The last couple of decades, in fact, have been characterized by an increased incidence of blast-TBI due to the widespread use of IEDs in wars and terrorist acts [167–169]. Due to the specific types of energies [170], physical dynamics [171], and temporospatial patterns [172] involved, the immediate pathologic consequences of blast-TBI, as well as their insidious and devastating long-term clinical and neuropsychiatric effects [173, 174], have taken on particular social, military, and scientific relevance. This special attention is also due to the prolonged duration of the conflicts in the Middle East, multiple lengthy deployments jointly to the trivialization of IEDs blast-TBI effects, which have produced an increased number of war veterans, and civilians, with a high rate of permanent morbidity mainly associated with neurological and psychiatric disorders [175]. Apart from the possible short- and long-term neurodegenerative consequences, blast-TBI pathology seems to represent, at least partially, one of the possible neurobiological bases by which it could be possible to explain some aspects of post-traumatic stress disorder (PTSD) diagnosed in some groups of individuals, the majority of whom are blast-affected service members and veterans [176, 177].

Numerous animal models have been employed to simulate blast-TBI and its possible consequences on the brain and other organs [178]. However, studies analyzing blast-TBI effects in human brains have been extremely rare. Apart from the 100-year-old manuscripts published by Mott in 1916 [27], which for the first time described brain lesions linked to blast-TBI, little has been published in the international medical literature until 2016, when distinct blast-TBI neuropathologic lesions were finally described [38]. These novel neuropathologic findings, which need confirmation by further larger clinicopathologic studies, show patterns of astrogliosis (glial scarring) localized at the level of the white-gray matter junction, subpial plate, and perivascular regions (Fig. 5c). This pattern emphasizes the interfaces between tissues at different densities, such as white and gray matter, between cerebrospinal fluid and brain, and between blood vessels and brain parenchyma. This interface astroglial scarring (IAS) pattern is different from neuroinflammatory and astroglial scarring patterns observed in other conditions, such as impact-TBI, drug abuse, or aging. It has been hypothesized that these new neuropathologic findings may eventually make possible the "visualization" (or at least part of it) of the so-called invisible wounds of war. The "invisible wound" is a term recently introduced to define those clinically evident and

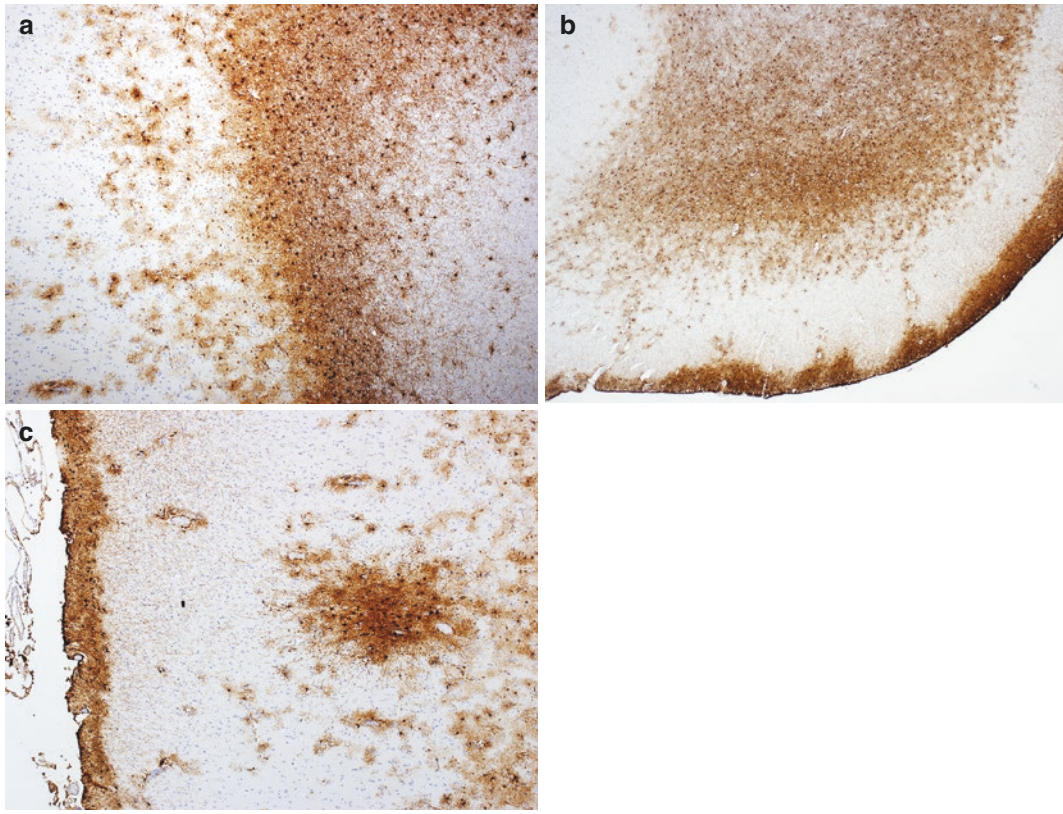

Fig. 5 (**a**–**c**) Blast-TBI. Example of interface astroglial scarring (IAS). White-gray matter (**a**), subpial (**b**), and perivascular IAS (**c**) in a subject exposed to blast-TBI. The pattern of interface astroglial scarring (interface between white-gray matter, cerebrospinal fluid-brain (subpial), and blood vessel-parenchyma (perivascular)) is detectable by performing immunohistochemistry for GFAP

assessable neuropsychiatric phenomena manifested by some war veterans for which no clear imaging, neurophysiologic, or specific biochemical correlates have been found [179, 180]. Although possibly related to clinical conditions differently named during the last century as "shell shock," "combat fatigue" syndrome [181, 182], or PTSD [183, 184], the "invisible wound" for many decades has been considered part of the postwar psychopathologic processes since it was apparently not related to any biological (neuropathologic) cause (http://www.nationalgeographic.com/healing-soldiers/blast-force.html).

Based on current evidence from a limited number of blast-TBI autopsy brains, it is not possible to definitively establish the extent that CTE, or some aspects of it, plays following such exposures. Future longitudinal clinicopathologic correlation studies analyzing a larger number of brains from blast-TBI cases are necessary to answer these questions. These prospective studies need to systematically collect detailed clinical, cognitive, genetic, and neuroimaging data. For example, detailed neurological and psychiatric evaluations, specific neuropsychological batteries, genotyping, diffusion tensor MRI, MRI tractography, PET scanning, etc. should be specifically employed for such investigations. It is also important to point out that two of the chronic cases described in Shively and coauthors [38] actually had a picture of mixed pathology that is IAS plus a degree of pTau pathology (CTE) [38]. Those two individuals were also the oldest persons in that study sample, and this could suggest that pTau pathology (i.e., CTE) can potentially be part of the later life and long-term neuropathologic

consequences due to blast events in veterans that have been exposed to single or multiple blasts on the battlefield. Finally, it is still unknown if factors, such as number of blasts, distance between the originating point of the blast and brain, intensity of the blast waves (related to the power of the explosive) versus brain volume/mass, preexisting conditions (war-related stress, neuroendocrine status pre- and post-blast exposure, genotypes, medications, etc.), and cognitive/synaptic reserve, could possibly be related to a "central nervous system threshold" above which a person exposed to blast begins to form, accumulate, and possibly spread IAS, pTau, or other abnormal protein aggregates throughout the brain.

Conclusions

The previous paragraphs have attempted to give a wide and general overview of the possible neuropathologic effects due different types of TBI, especially rTBI and its "newer" neuropathologic correlate CTE. As noticeable, there is still a lot to understand in terms of the possible relationships between TBI exposure and its neurological and psychiatric sequelae. It remains curious that, although TBI has accompanied humanity since its origin, research into its neuropsychiatric and neuropathologic consequences is still at its infancy. The aim of this chapter, other than providing a general description of the neuropathologic consequences of different types of TBI (sTBI, rTBI, blast-TBI), is to stimulate further clinical and basic research investigations that could shed light on the various molecular and cellular pathologic phenomena occurring after TBI, either sTBI, rTBI, or blast-TBI. Using the information gained, we may then develop more means to treat TBI-related clinical disorders, either through pharmacological or neurorehabilitative approaches. Furthermore, and very importantly, these studies will help to design new tools of protection against TBI exposure.

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Traumatic Brain Injury (TBI): Current Diagnostic and Therapeutic Challenges

Inbal Eshel and Donald W. Marion

Introduction

Traumatic brain injury (TBI) is the leading cause of death and disability among people in their first four decades of life. The National Center for Injury Prevention and Control estimates that 53,000 people (18.4/100,000 population) die each year from TBI-related injuries [1].

In spite of progress in the understanding and care of patients with TBI, this area remains fraught with challenges, from dissemination and implementation of known best practices to long-standing racial and financial inequalities which impact patient care and long-term outcomes. Gaps abound in our ability to maximize diagnosis and treatment, from the difficulties associated with identifying reliable biomarkers and pharmacotherapies to the timing, intensity, and types of rehabilitation needed to improve patient quality of life. Although calculators have improved gross prognostication, providing accurate education to patients and families remains more art than science. In addition, virtually none of the scores of promising preclinical drug trials for the treatment of severe TBI have resulted in successful clinical trials demonstrating benefit to injured patients. In spite of these many obstacles, this is an exciting time in brain injury research, as technology is rapidly evolving and practice-based evidence methodology is becoming more widespread, providing insights yet unknown. This chapter provides an overview of some of the current challenges in mild, moderate, and severe TBI diagnosis and treatment, as well as a look into the future of TBI, from the laboratory to the clinic.

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Mild Traumatic Brain Injury

Current Diagnostic Challenges and Trends

Mild TBI (mTBI) presents a unique diagnostic challenge because the neurologic signs and symptoms are typically subtle and require the patient to volunteer information and answer subjective questions about their recovery. In fact, the hallmark of mTBI, also known as concussion, is physiologic injury not associated with physical disruption or damage to central nervous system (CNS) tissues, at least as can be detected with conventional imaging studies, due to an external event that imparts a concussive energy to the brain. There is an associated alteration of consciousness with or without amnesia for the event. Concomitant symptoms may include headache, insomnia, dizziness, and/or diminished attention or reaction time. Unfortunately, the culture in subgroups of individuals most at risk for mTBI, such as high school and college athletes and

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active-duty military personnel, is to minimize or ignore symptoms and not be forthcoming about such symptoms so that they can quickly return to play or battle.

Timely reporting and diagnosis of mTBI is of critical importance because a person still symptomatic from an mTBI who sustains a second mTBI before full recovery from the first is at an increased risk of prolonged or permanent neurologic injury. In part, this is due to a significant mismatch of cerebral blood flow and metabolism immediately following a TBI which can be observed for several days [2]. In addition, compensatory sodium channel metabolism following a mild TBI imposes a significant metabolic burden on the axon; and this, too, may contribute to the vulnerability of the tissue to prolonged or permanent damage following a second impact. Ongoing white matter degeneration may occur for up to 10 years after injury in TBI survivors [3] and may include thinning of the corpus callosum with up to 25–30 percent loss of volume. Others have documented amyloid precursor protein and, to a lesser extent, neurofibrillary tangles, as frequent findings in persons with a history of multiple mTBIs who die from other causes [4]. The mTBIs appear to cause hyperphosphorylation and misfolding of tau protein leading to the formation of neurofibrillary tangles as well as stress granules. This pathology has been linked to the early onset of an Alzheimer's-like dementia known as chronic traumatic encephalopathy (CTE) and is most common with multiple mTBIs.

There is an urgent need for evidence-based diagnostic technology that will allow for the objective acute diagnosis of mTBI, especially in light of the potential for neurological and functional impact on long-term outcomes. The optimal test for the acute diagnosis of mTBI will likely include a combination of three or more tests of neurologic or physiologic dysfunction [5]. Toward this end, new and experimental diagnostic technology that can provide an objective evaluation for TBI is being developed in several areas, including subtle neurologic and physiologic abnormalities, electrophysiologic abnormalities, and imaging and molecular biomarkers. As many of these are still under development, an update on the current state of diagnosis of cognitive difficulties following mTBI will be provided prior to a description of these novel techniques.

Cognitive Deficits

Mild cognitive deficits, especially in executive functioning, are common following TBI, even in mTBI. These deficits can disrupt cognitive functioning as well as other aspects of behavior, including decision-making, motivation, and impulse control [6, 7]. Following mTBI, cognitive deficits are also seen in reaction time, attention, mental efficiency, processing speed, and delayed memory [8]. However, it should be noted that there is considerable variability across reviews in the effect sizes for specific domains, as concluded by a systematic review of meta-analytic reviews of the cognitive sequelae of mTBI [9].

The 2016 VA/DoD Clinical Practice Guideline for the Management of Concussion – Mild Traumatic Brain Injury [10] states that cognitive and/or neuropsychological testing should not be routinely obtained in the acute, subacute, or even post-acute period, because this is when most recovery can be expected and cognitive deficits are rapidly evolving. However, for some symptomatic patients in specific situations, cognitive and/or neuropsychological testing may be indicated during the first 30 days post-injury. If symptoms persist after 30–90 days, a functional, comprehensive cognitive assessment is recommended. As subtle cognitive changes may not readily appear with standard tools, a thoughtful combination of conventional standardized assessments, self-report, and ecologically relevant measures are recommended to build a treatment plan and make referrals to other rehabilitation specialists as needed. This process can be complex and relies on the clinician's willingness to move beyond traditional assessments and to acknowledge that even subtle areas of relative weakness may represent meaningful functional change.

Assessment tools for cognition vary widely, and many have not been standardized for use with individuals with mTBI. Individual clinicians are charged with selecting the best available tools based on patient characteristics and the

environment of care. To standardize initial mTBI evaluation for active-duty service members, the Military Acute Concussion Evaluation (MACE) was developed as a screening algorithm for use by all military medical personnel, including those with very basic medical training. The MACE is composed of three parts that include (1) a Standardized Assessment of Concussion (SAC), which is essentially a cognitive test of working memory, (2) an abbreviated evaluation of neurologic signs, and (3) a questionnaire about presenting symptoms typically associated with mTBI. Although the three parts of the MACE used together have not been formally validated, the SAC portion of the MACE has been in a cohort of civilians [11]. Its use currently is mandated as a first assessment for all service members who have a potentially concussive event, but there is some concern about the sensitivity and specificity of the cognitive portion of the MACE when administered more than 12 hours after the mTBI [12]. The Sport Concussion Assessment Tool (SCAT) 2 is a quasi-neurological exam that is slightly more standardized than the MACE, contains a symptom rating section on a continuum, and, most importantly, contains a balance test [13]. However, the SCAT2 requires considerably more time to administer than the MACE and may, therefore, not be as practical.

More recently, the military implemented an "incident-based" directive for the evaluation of service members at risk of mTBI which mandates mTBI evaluation for all those exposed to a blast or other potentially concussive events. While this circumvents the problem of service members not volunteering concussion-related symptoms, it does not address the lack of an objective diagnosis for mTBI. A similar problem exists for civilian athletic teams in making return-to-play decisions. In the most recent NCAA International Symposium on Concussion in Sport, experts concluded that management and return-to-play decisions remained very subjective – essentially a clinical judgment on an individual basis [13].

Computerized neurocognitive assessment tools (NCATs) have been developed as convenient sideline methods for assessing cognitive deficits associated with mTBIs. Ideally, baseline studies are obtained preseason, and the results of the individual's own baseline can then be compared to their post-injury studies. However, several studies of college football players and United States military service members have recently found that comparison of post-injury NCAT studies with normative data can be as sensitive as the individual's own baseline test in identifying cognitive deficits associated with a concussion [14–16]. In the military and pursuant to a congressional mandate, baseline NCATs are routinely obtained for deploying service members and are available for comparison with post-injury studies. A comprehensive set of clinical recommendations for the indications and conditions for in-theater, post-injury NCAT testing has been published by the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury and provides specific guidance to providers on how and when to use the tests. NCAT performance is independently influenced by environmental factors, especially sleep deprivation, fatigue, and medications; so such guidance should significantly improve the quality of the studies obtained in the military.

Physical Abnormalities

Mild TBI can result in a number of oculomotor problems manifesting as abnormal saccades, difficulty with smooth pursuit, or an abnormal vestibulo-ocular reflex. Interestingly, smooth-pursuit eye tracking has the potential to measure attention and working memory, as ocular movements can be tracked and quantified according to speed, direction, and delay, with much of the variation attributed to attention deficits. However, sleep deprivation and stress may confound the results. A recent study evaluated new technology that can efficiently assess eye movements, vestibular abnormalities, and balance difficulties that may be associated with concussion. This study found that optokinetic stimulation and gaze stabilization test scores together with a test for near-point convergence were a sensitive model for discriminating concussed athletes from healthy controls (accuracy = 94.4%, AUC = 0.951) without the need for expensive equipment [17].

Olfaction is also impaired in a large proportion of people affected by TBI, and this sense is very easy to test – a person smells a scented card and is asked to identify the smell. Association of olfactory injury with mTBI is not clear, however, and this may be a more common problem for those with moderate or severe TBI where the olfactory fibers are severed at the level of the cribriform plate. Damage to olfaction also can be caused by chemical or blast exposure to the airway making it nonspecific to TBI.

Physiologic Abnormalities

Autonomic dysfunction is a common acute manifestation of mTBI [18]. An automated system to monitor and analyze heart rate variability has been developed, but because heart rate variability also is seen with non-CNS trauma, it is not a very specific finding. Such a device would likely be most helpful for informing return to duty/play rather than as a diagnostic test. Moreover, it would likely be most useful as a component of a test battery that assessed other variables. Measurement of pupil size, and especially reactivity to light, is an alternative test of autonomic instability that also would require an automation and analysis package. A portable "pupillometer" has been developed but would need to be validated for mTBI, particularly because pupil abnormalities can be due to injury or compression of the optic or oculomotor cranial nerves in the absence of a mild TBI. Abnormalities with sweating have been described as an autonomic dysfunction associated with TBI, but clinically significant hyperhidrosis has only been reported in those with severe injuries [18].

Dizziness and balance disturbances are common problems associated with mTBI and were identified as among the top three most common acute manifestations of sports-related mTBI by NCAA sports medicine specialists [13]. It was recommended by this group that balance testing should be a component of any acute assessment of mTBI. The Balance Error Scoring System (BESS), which utilizes a foam plate on which you have to balance and includes an easy-to-use scoring system, was introduced as a practical test of balance that could be used on the sideline of an athletic competition or in combat medical facilities [19]. Sensitivity of the BESS to symptomatic mTBI has not been adequately studied, so it would have to be clinically validated.

Electrophysiology

Conventional EEG is most useful for evaluating brain death, seizures, and sleep disorders. Certain EEG changes could be unique to mTBI, but they have not been defined. A simplified cap-based, 12-lead dry electrode array with a highly automated detection analysis system has been developed, but there are concerns about obtaining good signal-to-noise ratio in the field. Sleep deprivation and diet also can affect EEG, along with external 60-cycle interference. Quantitative EEG (qEEG) has the potential to summarize the large amount of electrophysiologic data obtained from multiple leads over hours of monitoring. However, experience to date has shown that the study is highly sensitive to a variety of brain electrical activities, not all of which are pathologic and, therefore, not very specific. There also is a lack of standardization for obtaining and interpreting qEEG. Despite these shortcomings, a recent clinical trial of a qEEG device manufactured by BrainScope (Ahead 300) found that a negative evaluation with the device, when obtained within 72 hours of injury, corresponded with no structural injury visible on a CT scan with greater than 90% sensitivity [20]. Based in part on that study, the FDA has approved marketing the BrainScope Ahead 300 for use as an adjunct to standard clinical practice to aid in the evaluation of patients who are being considered for a head CT, who sustained a closed head injury within 72 hours, present with a Glasgow Coma Scale (GCS) score of 13–15, and are between the ages of 18 and 85 years.

Event-related potentials (ERPs), both auditory and visual induced, have been shown to be abnormal with mTBI. One of the most common TBI-induced abnormalities is the appearance of the P50 wave, which normally is suppressed. A portable ERP device has been developed and needs to be refined for field-deployable testing. There also is a need to validate ERPs in mTBI and determine if mTBI is associated with a well-

defined signature. Maximizing the signal-to-noise ratio and avoiding artifact is a primary concern with acquisition of high-quality, interpretable data. A recent study of ERP-based brain network activation (BNA) scores in healthy athletes found a wide range of BNA scores, suggesting that a single BNA score or set of BNA scores from a single after-injury test session may be difficult to interpret in isolation without knowledge of the athlete's own baseline BNA score(s) [21].

Structural and Functional Imaging

Imaging of TBI patients with computed tomography (CT), and more recently MRI, is standard practice for those with moderate or severe injuries and for concussed patients with severe or persistent symptoms or signs. In the acute setting, the primary concern is to identify intracranial mass lesions, such as hematomas that require immediate surgical evacuation. Structural imaging may also help explain neurologic signs and symptoms associated with TBI by revealing areas of the brain that have been damaged by the trauma.

Diffusion tensor imaging (DTI) has been refined as an MRI technique with potential to assess subtle axonal and white matter injury not detectable on conventional T1, T2, or FLAIR acquisition sequences. With DTI, some of the most useful data are focal measures of the fractional anisotropy (FA), apparent diffusion coefficient (ADC), and axial diffusivity (AD). Investigators have demonstrated a strong correlation between ADC values and verbal memory and processing speed – two cognitive areas frequently affected by mTBI – but recent studies have not found as clear an association of DTI abnormalities with post-concussive disorder. In their study of 63 service members who had a clinical diagnosis of mild, uncomplicated TBI and who underwent DTI within 90 days of their injury, MacDonald and coauthors found that only 18 (29 percent) had abnormalities on DTI that were consistent with multifocal traumatic axonal injury. More recent studies suggest that single and especially multiple concussions are associated with multifocal white matter abnormalities detectable with DTI as early as 8 days and as long as months or even years after the trauma [22, 23].

Functional MRI (fMRI) can be used to image the regional or local cerebral metabolic changes associated with motor or cognitive activity. Blood oxygen-level-dependent (BOLD) measurements following a cognitive challenge typically reveal enlargement of the area of BOLD activation, though not necessarily an increase in the intensity of the activation, following a mTBI. However, calibration of such fMRI studies is difficult, and there is substantial variability of study results. Specifically, test-retest reliability is poor, so multicenter trials are currently not possible [24]. Resting fMRI has recently been proposed as a more stable imaging protocol than cognitive challenge fMRI and has been found to be especially helpful for evaluating functional connectivity between various regions of the brain [25].

Near-infrared spectroscopy (NIRS) can be used to detect abnormal patterns of metabolic activity similar to fMRI as well as superficial hemorrhage following TBI [26]. Easy-to-use portable devices are available and are being used in studies of hemorrhage and task-related brain activation. Validation for use in detection of metabolic changes characteristic of mTBI is the challenge and may not be feasible with such subtle injury.

Several other imaging studies that provide valuable metabolic information, such as magnetic resonance spectroscopy and positron emission tomography (PET), are primarily research tools and will not have a practical role in the routine evaluation of TBI patients for the foreseeable future.

Molecular Biomarkers

Serum or whole blood biomarkers have been identified that are uniquely associated with TBI. Targeted proteins from neural tissue are furthest along the development path, but endothelial proteins also are associated with TBI. Ubiquitin C-terminal hydrolase L1 (UCH-L1) was first detected as a brain-specific protein more than 25 years ago and currently is being tested as a promising biomarker for mTBI [27]. S100B and

GFAP have the potential to predict inflammatory injury to glia and are both undergoing validation in humans [28–31]. Neuron-specific enolase (NSE) is associated with neuronal damage following TBI and manifests as elevated serum levels, but primarily with moderate or severe TBI [32, 33]. In addition, copper, ceruloplasmin, and cuprizone have been proposed as potential biomarkers because of a key role they play in transmembrane calcium transport [34]. Serum concentrations of peripherally produced apolipoprotein A-I (ApoA-I) are elevated within 6 hours of mTBI. The increase is specific to brain injury and associated with favorable short-term outcomes. Other promising candidates for serum protein biomarkers are Tau (total and phosphorylated), alpha II spectrin breakdown protein (SBDP145 generated by calpain, SBDP120 generated by caspase), and beta-amyloid precursor protein.

The temporal profiles of GFAP and UCH-L1 were recently evaluated in a large cohort of trauma patients seen at an emergency department. Their diagnostic accuracy was assessed overtime, both individually and in combination, for detecting mild to moderate TBI, traumatic intracranial lesions on head CT, and neurosurgical intervention. Both GFAP and UCH-L1 were detectable within 1 hour of injury. GFAP peaked at 20 hours after injury and slowly declined over 72 hours. UCH-L1 rose rapidly and peaked at 8 hours after injury and declined rapidly over 48 hours. GFAP performed consistently in detecting mild to moderate TBI, CT lesions, and neurosurgical intervention across 7 days. UCH-L1 performed best in the early post-injury period [35]. On February 14, 2018, the FDA permitted marketing of a test for serum levels of UCH-L1 and GFAP, labelled the "Brain Trauma Indicator" by the company, as an aid in the evaluation of concussion to help determine the need for a CT scan.

Metabolomics, transcriptomics, and unbiased proteomics are expected to reveal other protein and nonprotein biomarker candidates, including several inflammatory molecules. In addition, there currently are studies evaluating biomarkers in urine and saliva as alternative fluids for testing. Those fluids have the advantage of avoiding finger stick or venipuncture. But micromolar concentrations of the proteins being investigated are often undetectable in fluids other than serum or cerebrospinal fluid, and the latter is not practical to obtain in most settings. Serum concentrations of some of the promising molecular biomarkers, and especially those associated with the inflammatory response, can vary significantly with exposure to a myriad of environmental variables, such as sleep deprivation, diet, non-CNS injury, and medications; so the clinical context in which the posttraumatic testing occurs needs to be thoroughly defined.

Energy Sensors

Impact or blast dosimeters have been developed for detection of the degree and direction of mechanical energy exposure. The sensor data can be transmitted to a laptop computer or personal digital assistant (PDA) and allows providers to define the actual severity of impact to the helmet. Prototype devices are being used in high school and college football. However, there is some concern that while these detectors may reliably sense the energy imparted to the helmet, this may not reflect the energy imparted to the head because of independent movement of the helmet [36]. Several studies of high school and college football players found no significant relationship between impact biomechanics measures, including linear acceleration and rotational acceleration, and post-concussive symptoms or cognitive performance change scores on a computerized neurocognitive assessment test [36, 37].

Current Therapeutic Challenges and Trends

Despite variations in the estimates of the prevalence of long-lasting post-concussive symptoms, the potential for functional impact can no longer be underestimated. The importance of the consequences of mTBI was clearly emphasized by Seidl and colleagues [38] who found that individuals with mTBI report lower levels

of satisfaction with life as compared with the non-injured population. This was corroborated by the large Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK TBI) study, which found that over 40% of patients reported significantly reduced life satisfaction 1 year post-injury.

The TRACK TBI multicenter study followed a large cohort of mTBI patients (defined as Glasgow Coma Scale or GCS equal to 13 to 15) admitted to trauma center emergency rooms [39]. Approximately 80% of patients reported at least one post-concussive symptom at 1 year, and nearly one-quarter of patients experienced functional limitations at work or in daily activities 1 year post-injury. Recently, Theadom and colleagues [40] found that 47.9% of a group of individuals from New Zealand were experiencing four or more post-concussive symptoms 1 year post-injury.

Trends in the literature point to several groups thought to be most vulnerable to long-lasting post-concussive symptoms. Preexisting psychiatric comorbidities, prior history of brain injury, older age, female sex, and lower education levels, among others, are considered premorbid risk factors for poorer outcomes [40–42]. Losoi and colleagues [43] found that in previously healthy adults, patients with mTBI who were still experiencing mild post-concussion-like symptoms at 12 months after injury had a comorbid psychological diagnosis of depression, traumatic stress, or both. Although small sex differences have been found for some outcomes, it should be noted that sex differences as prognostic indicators for recovery have not been well studied [44].

In an attempt to bridge the current gaps, there has been a surge of research on cognitive rehabilitation (CR) over the past several years. In fact, of the almost 1000 articles related to cognitive rehabilitation in the PubMed database to date, almost one-third of these studies were published in the last 3 years [45]. There are now multiple randomized controlled trials relating to CR and mTBI, primarily targeting compensatory strategies for executive functions [46, 47]. At this time, although there is sufficient quality of evidence to establish the efficacy of CR for mTBI, there remains a great need for additional methodologically rigorous and large-scale studies, including comparative effectiveness studies (also known as practice-based evidence (PBE) studies), to further elucidate the optimal type, timing, and intensity of cognitive rehabilitation needed for patients exhibiting post-concussive cognitive impairment, as well as the characteristics of individuals who would most likely benefit from the intervention [48].

Unfortunately, recent literature has demonstrated stark differences in provider comfort with and knowledge about mTBI. Rose and colleagues [49] highlighted variability in physician knowledge in the care of persistent post-concussive symptoms, specifically in the perceived health risks, management practices, and access to multidisciplinary care. Another recent study found that medical students may be receiving inadequate training in mTBI/post-concussive syndrome [50]. Fluctuations in the post-concussive zeitgeist have further complicated the provider's role in guiding patients. Recommendations regarding post-concussive rest illustrate these fluctuations – the current literature suggests that the prolonged activity restrictions often prescribed may actually hinder long-term outcomes [51], as they limit and slow reengagement with the stimulating activities of daily living. Overall, as the literature continues to evolve, there is substantial room for growth in the education and training of medical professionals in the realm of mTBI, as these recommendations may impact long-term functional outcomes.

Innovative Therapies for Mild TBI

Patients with mild or moderate TBI often struggle with cognitive and behavioral deficits that can diminish their quality of life and limit their educational and employment opportunities. Several clinical trials of novel therapies for these post-concussive symptoms have been completed in the last few years and include hyperbaric oxygen (HBO), methylphenidate, amantadine, and armodafinil, as well as light therapy and transcranial direct-current stimulation (tDCS).

Hyperbaric Oxygen

Hyperbaric oxygen (HBO) for the treatment of persistent post-concussive symptoms has now been evaluated by several independent investigators and found not to provide benefit beyond that seen with the sham control group. A large multicenter, double-blind, sham-controlled clinical trial of 72 military service members with ongoing symptoms at least 4 months after mTBI was conducted with participants randomized 1:1:1 to 40 HBO sessions administered at 1.5 atmospheres absolute (ATA), 40 sham sessions consisting of room air at 1.2 ATA, or no supplemental chamber procedures. No difference between the HBO group and the sham group was observed (P = 0.70) [52]. Similar findings were observed in 60 military service members with persistent post-concussive symptoms with at least 1 combat-related mTBI who were examined in a single-center, double-blind, randomized, sham-controlled, prospective trial at the Naval Medicine Operational Training Center at Naval Air Station Pensacola. Over a 10-week period, volunteers received a series of 40 once-daily hyperbaric chamber compressions at 2.0 atmospheres absolute (ATA). Between-group testing of pre- and post-intervention means revealed no significant differences on individual or total scores on the Posttraumatic Stress Disorder Checklist – Military Version or Rivermead Post-concussion Symptom Questionnaire, demonstrating no significant effect for HBO at 1.5 or 2.0 ATA compared with the sham group [53]. A third study of 50 subjects with traumatic brain injury (TBI) exposed to 2.4 ATA breathing 100% oxygen vs. sham (1.3 ATA air) completing a total of 30 exposures also found no statistically significant differences between sham and treatment groups, although both groups improved [54].

Methylphenidate

Fatigue, irritability, and excessive sleepiness are common post-concussive symptoms. Several promising clinical trials have been completed for drugs that counter those problems.

The effects of methylphenidate, a CNS stimulant, on mental fatigue and pain were studied in 29 physically well, rehabilitated TBI victims, 28 with an mTBI and one with TBI and neck, shoulder, and head pain. Methylphenidate significantly decreased mental fatigue, as evaluated by the Mental Fatigue Scale ($p < 0.001$), and the effects on mental fatigue were dose dependent [55]. A second study evaluated two different dosages of the drug with regard to post-TBI mental fatigue, pain, and cognitive functions. Fifty-one subjects were included, and 44 completed the study. The treatment continued for 12 weeks, including three treatment periods with no medication for 4 weeks, administration of low-dose methylphenidate (up to 5 mg × 3) for 4 weeks, and administration of normal-dose methylphenidate (up to 20 mg × 3) for a further 4 weeks. Significantly reduced mental fatigue, assessed with the Mental Fatigue Scale (MFS), and increased information processing speed (coding, WAIS-III) were detected. The SF-36 vitality and social functioning scales were also improved significantly. The positive effects of treatment were dose dependent, with the most prominent effects being at 60 mg methylphenidate/day spread over three doses [56].

Amantadine

The effect of amantadine, a dopamine reuptake inhibitor, on reducing irritability and aggression was investigated in 76 individuals greater than 6 months post-TBI referred for irritability management. Amantadine 100 mg every morning and at noon was shown to be an effective and safe means of reducing frequency and severity of irritability and aggression among individuals with TBI [57]. A separate trial of 168 persons ≥6 months post-TBI with irritability evaluated either amantadine 100 mg twice daily or equivalent placebo for 60 days. Observer ratings between the two groups were not statistically significantly different at day 28 or 60; however, observers rated the majority in both groups as having improved at both intervals. There was clearly a large placebo effect [58].

Armodafinil

The efficacy and tolerability of armodafinil, a wakefulness promoting agent with unclear mechanism, was evaluated in 117 patients with excessive sleepiness following mild or moderate

TBI. Patients received armodafinil (50, 150, or 250 mg/day) or placebo for 12 weeks followed by an optional 12-month open-label extension. At 250 mg/day the drug significantly improved sleep latency in patients with excessive sleepiness associated with mild or moderate TBI [59].

Atomoxetine

Atomoxetine, a selective norepinephrine reuptake inhibitor with a primary indication for attention dosed at 40 mg twice a day for 2 weeks, compared to placebo, was evaluated in 55 adult participants with a history of a single moderate to severe TBI, who were at least 1 year from injury and with self-reported complaints of attention difficulties. Individuals with attention difficulty following TBI did not significantly improve scores on measures of attention, the CDR Power of Attention domain, or the Stroop Interference score [60].

Light Therapy

In addition to pharmacotherapy, a recent study suggests that light therapy may benefit concussed patients suffering from fatigue. The efficacy of 4 weeks of home-based light therapy, 45 min/morning, with short-wavelength (blue) light therapy, compared with yellow light therapy containing less photons in the short-wavelength range and a no treatment control group (n = 10 per group), was investigated in patients with TBI who self-reported fatigue and/or sleep disturbance. After controlling for age, gender, and baseline depression, treatment with high-intensity blue light therapy resulted in reduced fatigue and daytime sleepiness during the treatment phase, with evidence of a trend toward baseline levels 4 weeks after treatment cessation. These changes were not observed with either the lower-intensity yellow light therapy or no treatment control conditions [61].

Moderate and Severe TBI

Current Diagnostic Challenges

Patients with moderate and severe TBI typically have obvious neurologic signs and symptoms, and the brain injury can be identified utilizing conventional imaging studies, such as CT scanning. As such, diagnosis of moderate and severe TBI is fairly straightforward. Complexities abound, however, in making prognostic decisions and subsequently providing education to patients and families with moderate and severe brain injuries. To address the challenges in prognostic assessment and family counseling, researchers have developed prognostic models: the Corticosteroid Randomization After Significant Head Injury (CRASH) and the International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury (IMPACT) [62, 63]. Iorio-Morin and colleagues developed a free TBI prognosis calculator application [64] for mobile devices based on the Medical Research Council (MRC) CRASH trial model. The prognosis calculator identifies the key demographic, clinical, and radiologic variables needed to provide an estimation of 14-day mortality and 6-month mortality and morbidity. Although this line of research represents a significant contribution to prognostication for severe brain injuries, it should be noted that it provides only a gross estimate of morbidity and that the prognostic calculator may in fact overestimate the risk of mortality and poor outcomes [65]. Therefore, while these calculators can act as adjuncts to prognostic assessment, they must be used with caution.

Overall, while there is a greater understanding of the key factors that are likely to influence prognostication in moderate and severe brain injuries, there remains relatively little to guide clinicians working with individual patients and their families to guide their expectations along the path to recovery. This gap is being addressed in part by the American Congress of Rehabilitation Medicine Disorders of Consciousness Task Force, which has developed minimal competency guidelines for the rehabilitation of patients with disorders of consciousness. Until these guidelines are published and other work is done to promote greater standards of care for this population, "inconsistent, inaccurate, and inappropriate care" [66] is widespread and raises a host of ethical considerations.

Current Therapeutic Challenges

Racial and socioeconomic disparities must be acknowledged as significant barriers to high-quality care, as they have profound consequences on patient outcomes. Insurance coverage and race may strongly influence access to intensive rehabilitative services. Meagher and colleagues [67] found that adult black and Hispanic patients with TBI are significantly less likely to receive intensive rehabilitation than non-Hispanic, white patients. Results from a large practice-based evidence study (N = 2130) illustrate the way in which these disparities may impact the translation of best practices into reality [68]. Horn and colleagues [68] found that the number of days from injury to acute rehabilitation admission can have a significant impact on the patient's functional outcome at discharge. More specifically, most patients who experienced a greater number of days from injury to rehabilitation hospital admission had a host of challenges later on compared with patients with shorter days from injury to admission, including longer length of stay in rehabilitation, lower motor and cognitive Functional Independence Measure (FIM) scores at discharge, and lower 9-month FIM scores, beyond measures of injury severity. Surprisingly, these researchers also found that adult black and Hispanic individuals with the same insurer (e.g., Medicare) as their white counterparts were subject to these disparities in access to intensive rehabilitation. Gardizi and colleagues [69] found that the cumulative effect of self-reported medical comorbidities and type of insurance coverage predict disability beyond typical prognostic factors.

Innovative Therapies for Severe TBI

Current care of patients with a severe TBI is focused on the early identification of metabolic and physiologic dysfunction and effective treatment of that dysfunction so as to limit, or prevent, permanent neurologic and functional damage. The pathobiology of TBI involves multiple biochemical, metabolic, inflammatory, and even genetic mechanisms. Failure of most previous therapies to benefit patients with TBI is likely because they targeted only one or a few of these mechanisms responsible for secondary brain injury rather than others that played a significant role. Drugs or other therapies most likely to be successful in future clinical trials must target multiple key mechanisms responsible for secondary brain injury. Such therapies could theoretically include HBO, erythropoietin (EPO), progesterone, and therapeutic moderate hypothermia.

Hyperbaric Oxygen

One recent study of severe TBI patients evaluated combined HBO/normobaric hyperoxia (NBH) treatments and found that they significantly improved markers of oxidative metabolism in relatively uninjured brain as well as pericontusional tissue, reduced intracranial hypertension, and demonstrated improvement in markers of cerebral toxicity. Brain tissue partial pressure of O2 (PO2) levels were significantly increased during and following combined HBO/NBH treatments in both the non-injured and pericontusional brain. Microdialysate lactate/pyruvate ratios were significantly decreased in the non-injured brain in the combined HBO/NBH group as compared with controls. However, no long-term improvement in functional outcomes was demonstrated as a result of treatment [70].

Erythropoietin

Erythropoietin, a cytokine for erythrocyte precursors in the bone marrow, has been shown in preclinical studies of several models of TBI to have neuroprotective properties, acting via EPO receptors on cerebrovascular endothelia and ischemic neurons. The drug was shown to reduce hippocampal cell loss, enhance angiogenesis and neurogenesis, and improve functional outcome following TBI in rats [71]. However, the results of clinical trials conducted to date have not supported the use of this therapy. Recently, it was investigated in a double-blind, placebo-controlled trial undertaken in 29 centers in seven countries. Within 24 hours of brain injury, patients were randomly assigned to erythropoietin (40,000 units

subcutaneously) or placebo once per week for a maximum of three doses. Erythropoietin did not reduce the number of patients with severe neurologic dysfunction (Glasgow Outcome Scale-Extended or GOS-E score of 1 to 4) or increase the incidence of deep venous thrombosis of the lower limbs [72]. In a separate randomized clinical trial of 200 patients (erythropoietin, n = 102; placebo, n = 98) with closed head injury who were unable to follow commands and were enrolled within 6 hours of injury, erythropoietin or placebo was initially dosed daily for 3 days and then weekly for 2 more weeks (n = 74). In patients with closed head injury, neither the administration of erythropoietin nor maintaining hemoglobin concentration of greater than 10 g/dL resulted in improved neurological outcome at 6 months [73].

Progesterone

Preclinical studies have found that progesterone decreases inflammation, reduces oxidative stress, decreases edema, and improves functional outcomes following experimental TBI [74]. These studies have also found a significant reduction in lesion volume associated with progesterone treatment of either cerebral ischemia or TBI, in a dose-dependent manner [75]. However, results of clinical trials do not support continued use of this therapy. A multinational placebo-controlled trial was completed in which 1195 patients, 16 to 70 years of age, with severe TBI and at least one reactive pupil were randomly assigned to receive progesterone or placebo. Dosing began within 8 hours after injury and continued for 120 hours. Proportional odds analysis with covariate adjustment showed no treatment effect of progesterone as compared with placebo [76]. A second double-blind, multicenter clinical trial was completed in which 882 patients with severe, moderate to severe, or moderate acute TBI were randomly assigned to intravenous progesterone or placebo, with the study treatment initiated within 4 hours after injury and administered for a total of 96 hours. The trial was stopped for futility with respect to the primary outcome. There was no significant difference between the progesterone group and the placebo group in the proportion of patients with a favorable outcome (relative benefit of progesterone, 0.95; 95% confidence interval [CI], 0.85 to 1.06; p = 0.35). Phlebitis or thrombophlebitis was more frequent in the progesterone group than in the placebo group [77].

Therapeutic Moderate Hypothermia

Therapeutic moderate hypothermia (32–33 degrees C for 48 hours or more) continues to be investigated because of its potential to ameliorate multiple mechanisms of secondary injury and because of the success of clinical trials for out-of-hospital cardiac arrest and neonatal hypoxic-ischemic encephalopathy. Although several large clinical trials in TBI patients have not found benefit of cooling, those trials have been criticized for patient selection based only on GCS, delayed initiation of cooling, short duration of cooling, inter-center variation in patient care, and relatively rapid rewarming. To address some of these limitations, a multicenter randomized, controlled trial in patients with severe TBI (GCS of 4 to 8) was conducted. Patients were randomly assigned (2:1 allocation ratio) to either therapeutic hypothermia (32–34 °C, n = 98) or fever control (35.5–37 °C, n = 50). Patients with therapeutic hypothermia were cooled as soon as possible for ≥72 hour and rewarmed at a rate of <1 °C/day. At 6 months after injury, there were no significant differences in the likelihood of poor neurological outcome (relative risk [RR] 1.24, 95% confidence interval [CI] 0.62–2.48, p = 0.597) or mortality (RR 1.82, 95% CI 0.82–4.03, p = 0.180) between the two groups [78]. A separate study compared adults (n = 387) with an intracranial pressure of more than 20 mm Hg despite stage 1 treatments (including mechanical ventilation and sedation management) to standard care (control group) or hypothermia (32 to 35 °C) plus standard care. The adjusted common odds ratio for the GOS-E score was 1.53 (95% confidence interval, 1.02 to 2.30; p = 0.04), indicating a worse outcome in the hypothermia group than in the control group. A favorable outcome (GOS-E score of 5 to 8, indicating moderate disability or good recovery) occurred in 26% of the patients in the hypothermia group and in 37% of the patients in the control group (p = 0.03) [79]. A third study

completed in Japan from 2002 to 2008 also did not find efficacy of hypothermia when compared with a fever control group. In a secondary analysis, favorable outcomes were observed in young patients (≤50 years old) with evacuated mass lesions treated with hypothermia (77.8%) compared with 33.3% for the fever control group. Patients with diffuse injury who were treated with therapeutic hypothermia, however, had significantly higher mortality than patients treated with fever control [80].

Stem Cells

In addition to therapies targeting mechanisms of secondary injury, stem cells, singularly or in combination with biomaterials that act as a scaffold, are being investigated in preclinical studies to reduce brain injury via neuroprotection and promote brain remodeling via angiogenesis, neurogenesis, and synaptogenesis [81]. Tissue engineering, using a bioactive scaffold, can help to counter some of the hostile host inflammatory factors that have limited the successful structural and functional integration of these transplants in the past. The scaffold can chaperone donor cells into the brain and promote differentiation of the cells into neurons, astrocytes, or oligodendrocytes as might be appropriate for the specific needs of the brain location. The cell source (i.e., embryonic, umbilical cord, bone marrow), scaffold composition, and delivery methods are all areas of intense investigation. In addition, enriched environment and voluntary physical exercise show promise in promoting functional outcome after TBI and should be evaluated alone or in combination with other treatments as therapeutic approaches for TBI [82]. Some of these concepts were tested in a clinical study of umbilical cord mesenchymal stem cell transplantation in 40 patients with TBI. Patients were randomly assigned to a stem cell treatment group or a control group. Patients in the stem cell treatment group underwent four stem cell transplantations via lumbar puncture. The Fugl-Meyer Assessment results demonstrated an improvement in upper extremity motor sub-score, lower extremity motor sub-score, sensation sub-score, and balance sub-score in the stem cell transplantation group at 6 months after the transplantation ($p < 0.05$). The FIM results also exhibited significant improvement ($p < 0.05$) in the patient self-care sub-score, sphincter control sub-score, mobility sub-score, locomotion sub-score, communication sub-score, and social cognition sub-score [83]. However, this was a small study, and results will need to be replicated in an appropriately powered phase III clinical study before they should be considered valid.

Transcranial Direct-Current Stimulation

Transcranial direct-current stimulation has shown promise in some studies for improvement of memory and attention following severe TBI. The cumulative effects of anodal tDCS on EEG oscillations and neuropsychological tests among patients with traumatic brain injury (TBI) undergoing subacute neurorehabilitation were assessed in 26 patients. Following a TBI, there typically is diffuse slowing of EEG activity, with increased irregular theta activity. Theta rhythms, which are commonly associated with meditative, drowsy, hypnotic, or sleeping states, were significantly reduced for active tDCS patients following the first tDCS session. Delta waves, usually associated with deep sleep, decreased, and alpha waves, important in brain network coordination and communication, increased, both significantly, for the active tDCS group after ten consecutive tDCS sessions. No significant changes were seen for the sham group. Decreases in delta were significantly correlated with improved performance on neuropsychological tests for the active tDCS group to far greater degree than for the sham group. Participants in the active tDCS group who had excess slow EEG activity in their initial recordings showed greater improvement on neuropsychological tests than other groups. Results suggest that ten anodal tDCS sessions may beneficially modulate regulation of cortical excitability for patients with TBI [84]. In a separate study, cumulative anodal transcranial direct-current stimulation (A-tDCS) of the left dorsolateral prefrontal cortex (DLPFC) was studied to determine if it could enhance rehabilitation of memory and attention in 23 adult patients, 4–92 months post-severe TBI randomly allocated to 2

groups. The experimental group received A-tDCS (10 minutes; 1 mA; in the DLPFC), followed by rehabilitative cognitive training, daily for 15 days. Controls received A-tDCS for 25 seconds (sham condition) with the same rehabilitation. In contrast to previous studies, this study did not provide sufficient evidence to support the efficacy of repeated A-tDCS for enhancing rehabilitation of memory and attention in patients after severe TBI [85].

Tranexamic Acid

Approximately 20–30% of patients with posttraumatic contusions will hemorrhage into those contusions during the first 24–48 hours after a TBI, often resulting in deterioration in their neurologic status and the urgent need for surgical evacuation of the mass. Recently, the US military has found that tranexamic acid (TXA) can help reduce bleeding from battlefield trauma. TXA is an antifibrinolytic agent that is FDA approved for menorrhagia and other indications associated with a high risk of bleeding. In a study of 274 hospitals in 40 countries, patients were allocated to TXA (n = 10,096) and to placebo (n = 10,115), of whom 10,060 and 10,067 patients, respectively, were analyzed. All-cause mortality at 28 days was significantly reduced by TXA [1463 patients (14.5%) in the TXA group vs. 1613 patients (16.0%) in the placebo group; relative risk (RR) 0.91; 95% confidence interval (CI) 0.85 to 0.97; p = 0.0035]. The risk of death due to bleeding was significantly reduced [489 patients (4.9%) died in the TXA group vs. 574 patients (5.7%) in the placebo group; RR 0.85; 95% CI 0.76 to 0.96; p = 0.0077]. Early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost-effective. It recently has been determined that treatment beyond 3 hours of injury is unlikely to be effective [86]. To determine the effectiveness and safety of TXA in preventing progressive intracranial hemorrhage in TBI, 238 patients older than 16 years with moderate to severe TBI (post-resuscitation GCS of 4 to 12) who had a brain CT scan within 8 hours of injury and in whom there was no immediate indication for surgery were enrolled. The treatment was a single dose of 2 grams of TXA in addition to other standard treatments. Progressive intracranial hemorrhage was present in 21 (18%) of 120 patients allocated to TXA and in 32 (27%) of 118 patients allocated to placebo, and this difference was not statistically significant [87].

Looking Ahead: Future Therapies and Techniques

Advances in technology and research methodology indicate that future therapies may look different than the ones we have access to now.

Virtual Reality

Virtual reality (VR) will likely become increasingly prevalent in military [88] and civilian TBI assessment and treatment as the technologies become smaller and increasingly customizable [89]. Current use of VR is constrained both by the technology itself and by availability/resources. Although evidence is still limited, VR has the potential to fill current gaps in service provision by making therapy more available to individuals with limitations in geographical access to care and/or finances [90].

Practice-Based Evidence

It is widely acknowledged that traditional randomized, controlled trials are not always ideal for rehabilitation research. Challenges with the traditional "gold standard" include decreased ecological validity, limited "head to head" comparisons as individual characteristics vary widely, and limited ability to notice new associations within a multi-treatment context, which is a commonplace reality of intervention. Researchers are experimenting with a variety of methodologies to circumvent these challenges, one of which is "practice-based evidence" (PBE) [91]. PBE studies are observational, cohort, prospective studies, in which large samples and diverse patient sources and samples are utilized to collect detailed, standardized documentation of interventions. PBE

can confirm outcomes associated with specific treatments and can ultimately translate into changes in clinical practice patterns.

Summary

The optimal test for the acute diagnosis of mTBI remains elusive; however, a variety of efforts are underway, with the common goal of identifying an objective diagnostic tool that will likely need to incorporate a combination of three or more tests of neurologic or physiologic dysfunction. The long-term functional impact of mTBI is of growing concern; further research is needed to elucidate the optimal type, timing, and intensity of rehabilitation. Current therapeutic trials for patients with mTBI have focused on alleviating fatigue and sleepiness, and there appears to be a role for methylphenidate and armodafinil in some of these patients.

Moderate and severe TBI prognostication presents hardships for providers, patients, and family members. At the same time, longstanding socioeconomic and racial inequalities have the potential to impact the type of care received and, subsequently, long-term outcomes. Unfortunately, no clinical trials for novel treatments of severe TBI have been successful to date. HBO therapy also has been evaluated in multiple clinical trials for both mild/moderate and severe TBI patients and does not result in improved outcomes beyond what is observed in sham controls. Novel treatment approaches and research methodologies may foster future advances.

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Appendix

Theresa Brown Lattimore and Yll Agimi

TBI Diagnostic Coding Practices and Procedures

ICD-10

The International Classification of Diseases (ICD), developed by the World Health Organization (WHO), is the international "standard diagnostic tool for epidemiology, health management and clinical purposes" [1]. The ICD is a hierarchy of disease diagnostic codes for the classification of diseases, signs, symptoms, complaints, and external causes of injury or disease [2]. Used by healthcare providers, insurers, researchers, and public health agencies, the ICD acts as the diagnostic classification standard for all clinical and research purposes and serves as the international standard for the identification of health trends and the reporting of disease statistics [1].

ICD-10-CM

In the United States, the National Center for Health Statistics (NCHS) was tasked with developing a clinical modification of the ICD classification for morbidity purposes. The resulting International Classification of Diseases, 10th Revision Clinical Modification (ICD-10-CM), for use in the United States on or after October 1, 2015,[1]1 is based on and conforms to ICD-10, the statistical classification of disease published by the WHO [3]. The ICD-10-CM improved the ICD-10 by adding information relevant to ambulatory and managed care encounters, expanding the coding for injuries and reducing the number of codes required to describe a condition, through the creation of a combination of diagnosis and symptom codes. Furthermore, the ICD-10-CM added the sixth and seventh characters, providing additional specificity to assigned codes [3].

Official guidelines for coding and reporting, using ICD-10-CM, is provided by the Centers for Medicare and Medicaid Services (CMS) and the NCHS, approved by the members of the cooperating parties for the ICD-10-CM, which, in addition to the CMS and NCHS, also include the American Hospital Association (AHA) and the American Health Information Management Association (AHIMA). Adherence to these guidelines when assigning ICD-10-CM diagnosis codes is required under the Health Insurance Portability and Accountability Act (HIPAA) [4].

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[1]Note: Navy Fleet Forces will continue to use ICD-9 when ICD-10 is not available.

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ICD-10-CM Military Health System

Within the US Department of Defense (DoD), the Joint Coding Guidance Working Group (JCGWG) developed guidance for DoD documentation and coding for inpatient and professional services using ICD-10-CM for use in the Military Health System (MHS) [5]. While the MHS coding guideline adheres to national ICD-10-CM guidelines, the JCGWG guidelines provide specific guidelines for the use of ICD-10-CM for coding of ambulatory and professional services encounters at MHS Medical Treatment Facilities (MTFs) and takes precedence over all other standards [5]. The JCGWG, composed of DoD documentation and coding experts, is responsible for guidance revisions as well as annual guidance updates.

ICD-10-CM (MHS) Coding Overview

Within the ICD-10-CM coding system, there are three major types of codes: diagnostic, procedural, and evaluation and management (E&M). *Diagnostic codes* classify diseases, signs, symptoms, complaints, and a variety of other information. Diagnostic codes may also collect information on nonmedical reasons for seeking care as well as cause of injury information. *Procedural codes* use the Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT®) to report services, procedures, supplies, equipment, and devices provided to patient. *E&M coding*, a subject of HCPCS procedure codes, are codes that describe services not associated with a procedure or therapy provided during a healthcare encounter. These codes classify services provided and indicate level of service. The remainder of this chapter focuses specifically on the diagnostic codes.

The ICD-10-CM coding system uses codes of three- to seven-digit alphanumeric characters in contrast to ICD-9-CM codes that used three- to five-digit numeric and alphanumeric codes. Historically, a number of ICD-9-CM codes were modified for special use in the DoD through the addition of extender codes known as "DoD extender" codes. With the transition to ICD-10-CM, this practice has ceased. In lieu of "DoD extender" codes, DoD has added DoD unique codes to meet special DoD data collection requirements. These DoD unique codes are easily identifiable as they are all seven characters long, begin with "DoD," and do not have a decimal [5].

Traumatic Brain Injury Coding in DoD

In the MHS, TBI is defined as a "traumatically induced structural injury and/or physiological disruption of brain function, as a result of an external force, that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event: any period of loss of or decreased level of consciousness; any loss of memory for events immediately before or after the injury; any alteration in mental state at the time of the injury (e.g., confusion, disorientation, slowed thinking, etc.); neurological deficits (e.g., weakness, loss of balance, change in vision, praxis, paresis/plegia, sensory loss, aphasia, etc.) that may or may not be transient; and intracranial lesion" [6].

External forces is defined as any of the following events: the head being struck by an object, the head striking an object, the brain undergoing an acceleration/deceleration movement without direct external trauma to the head, a foreign body penetrating the brain, forces generated from events such as a blast or explosion, or other forces yet to be defined. While the above criteria define the event of a TBI, not all individuals exposed to an external force will sustain a TBI; however, any person who has a history of such an event with immediate manifestation of any of the above signs and symptoms is considered to have sustained a TBI.

In the DoD, TBI is further grouped into four major groups. They include concussion/mild TBI (mTBI), moderate TBI, severe TBI, and penetrating TBI. The clinical and diagnostic criteria used to determine classification of TBI include results from structural imaging, length of loss of consciousness (LOC), length of alteration of consciousness/mental state (AOC), presence of post-traumatic amnesia (PTA), and Glasgow coma scale score within the first 24 h.

Specifically, *concussion/*m*TBI* is characterized by the following: confused or disoriented state,

Table A.1 Classification of TBI severity

Criteria	Mild	Moderate	Severe
Structural imaging	Normal	Normal or abnormal	Normal or abnormal
Loss of consciousness (LOC)	0–30 min	>30 min and <24 h	>24 h
Alteration of consciousness/mental state (AOC)	A moment up to 24 h	>24-h severity based on other criteria	
Post-traumatic amnesia (PTA)	0–1 day	>1 and <7 days	>7 days
Glasgow coma scale (best available score in the first 24 h)	13–15	9–12	<9

which lasts less than 24 h, loss of consciousness for up to 30 min, or memory loss lasting less than 24 h. Penetrating TBIs are excluded from this group. A computerized tomography (CT) scan is not indicated for most patients with an mTBI. However, if obtained, then it is normal.

Moderate TBI is characterized by the following: confused or disoriented state which lasts more than 24 h, loss of consciousness for more than 30 min but less than 24 h, memory loss lasting greater than 24 h but less than 7 days, or meets criteria for mTBI except when an abnormal CT scan is present. Penetrating TBIs are excluded from this group. A structural brain imaging study may be normal or abnormal.

Severe TBI is characterized by the following: confused or disoriented state which lasts more than 24 h, loss of consciousness for more than 24 h, or memory loss for more than 7 days. Penetrating TBIs are excluded from this group. A structural brain imaging study may be normal but is usually abnormal.

Penetrating TBI, or open head injury, is characterized by the following: a head injury in which the scalp, skull, and dura mater (the outer layer of the meninges) are penetrated. Penetrating injuries can be caused by high-velocity projectiles or objects of lower velocity, such as knives, or bone fragments from a skull fracture, that are driven into the brain (Table A.1).

Background on Traumatic Brain Injury Coding in the DoD

For monitoring and reporting purposes, traumatic brain injuries are defined by a system of approximately 200 ICD-10-CM codes and DoD unique codes. The code list identifying clinical conditions indicative of TBI was originally developed in August 2008 by policy makers and medical experts from all DoD services and from several DoD and Health and Human Services (HHS) agencies [7]. The Defense and Veterans Brain Injury Center (DVBIC) monitors the TBI definition for the MHS and, together with the above agencies, has revised the original definition several times since its creation. The current code set, published in December 2015, was the result of collaborations and consensus of the TBI Community of Interest, the Defense and DVBIC, the Armed Forces Health Surveillance Branch (AFHSB), and the Centers for Disease Control and Prevention (CDC).

Common Codes Used for TBI Encounters

TBI Diagnostic Codes

For TBI diagnostic codes, the first six characters represent the code specific to the diagnosis, and the seventh character (letter) specifies whether the diagnosis involves the initial medical encounter (A), subsequent encounter related to the initial diagnosis (D), or a *sequela* of the initial diagnosis (S). When coding fracture injuries, codes also include (A) initial encounter for closed fracture and (B) initial encounter for open fracture [7].

Concussion/mTBI

Initial mTBIs can be coded with a number of codes, with frequent codes including S06.0X0A (concussion with no loss of consciousness (LOC)), S06.0X1A (concussion with loss of consciousness of 30 min or less), and S06.0X9A

(concussion with loss of consciousness of unspecified duration). The latter is grouped under concussion/mTBI due to the current practice of assigning the lowest group severity level to group codes with unspecified loss of consciousness information [7]. According to DoD criteria, common forms of concussive injuries with loss of consciousness of 30 min or less indicate a mild form of TBI. For example, the diagnostic code for an initial visit related to a concussion with no LOC will be coded as S06.0X0A. However, while duration of LOC is an important criteria to assign TBI severity to a sustained injury, injuries without LOC or LOC of 30 min or less may be classified as moderate or severe TBIs, such as S06.310A (contusion and laceration of right cerebrum without LOC) or S06.311A (contusion and laceration of right cerebrum with LOC of 30 min or less) when additional information suggests a higher severity classification. Furthermore, a number of injuries involving closed or skull fractures of unknown type, notably type I, III, and unspecified occipital condyle fracture as well as fractures of other specified skull and facial bones, are classified as mTBI. Codes S06.0X2 through S06.0X8, concussive injuries with LOC of 31 min or higher, or those ending in death, are not to be used when classifying TBI as mild. Effective October 1, 2016, codes S06.0X2 through S06.0X8 were deleted as part of the 2017 ICD-10-CM changes [8].

Moderate/Severe TBI

Approximately 160 ICD-10-CM codes can be used to indicate moderate or severe TBI. Codes include injuries denoting traumatic cerebral edema, diffuse traumatic brain injury, contusion and laceration of cerebrum injuries, and other intracranial injuries. Frequent moderate and severe TBI codes may include S06.89 series (other specified intracranial injury) and S06.9X series (unspecified intracranial injury), when there is no other intracranial injury. Diffuse traumatic brain injury codes (S06.2X series) are also frequently used. Of note, ICD-10-CM codes S09.8 (other specified injuries of the head) and S09.90 (unspecified injury of the head) are not used to monitor and report TBI. Emerging epidemiological evidence suggests lack of specificity for these codes, with their use often not indicating TBI [9]. This practice is consistent with the Centers for Disease Control and Prevention (CDC). Furthermore, the severity of ICD-10-CM codes S04.02-S04.04 (injury to optic chiasm and optic tract) was deemed more likely than not to be associated with a "severe" TBI [10].

Penetrating TBI

Diagnostic codes denoting open skull fractures (S02 series), including fractures of the vault of the skull; fracture of the base of the skull; open type I, II, and III occipital condyle fractures; and other open fractures of the skull and facial bones are used to classify injury as penetrating injury. ICD-10-CM code S02.8 (fracture of other specified skull and facial bones) and S07.1 (crushing injury of the skull) were newly added to the ICD-10-CM TBI code set in an effort to be consistent with the CDC. ICD-10-CM code S01.90X (unspecified open wound of unspecified part of the head) is not used to denote penetrating TBI. According to the TBI case definition working group, this code may represent a minor injury such as a scalp laceration and is deemed to lack sufficient specificity to classify an injury as a TBI for the purposes of DoD TBI surveillance [11].

Coding Practices at Patient Encounters

TBI Screening Codes

Coding practices regarding the use of DoD unique screening codes, including TBI screening codes, are determined by MHS JCGWG. However, due to the clinical care and reporting and documentation purposes of these codes, varying interpretations of their use exist. While the MHS JCGWG guide suggests that TBI screening codes are only to be used with asymptomatic patients, since the presence of symptoms renders the encounter diagnostic, others suggest that screening codes be used at all encounters, whenever such a screening is conducted [12]. The former

advises that documentation of TBI screening codes should be based on whether the encounter resulted in the diagnosis of TBI, whereas the latter proposes that monitoring of screening practices would be impossible without the full documentation of screening codes used, positive or negative, as discussed below.

Positive Screening

However, others argue that DoD0122 codes should be used whenever the screening results indicate it, even if this occurs in the same encounter as the initial diagnosis [12]. This discussion is further complicated within the military, due to common utilization of medics and hospital corpsmen for the performance and documentation of TBI screenings.

Negative/Declined Screening

In addition to DoD0122 (screening for traumatic brain injury (TBI), positive findings) code, codes indicating negative or otherwise inconclusive screening results exist. According to MHS JCGWG, these codes are to be used when patient does not show symptoms of TBI, otherwise leading to a TBI diagnosis, and are coded at the initial evaluation when a diagnosis of TBI is not assigned. However, others suggest that given the importance of screening practices for clinical care as well as monitoring and reporting purposes, it is important to document if TBI screening was performed. In the event that a screening was performed, and the results were not positive, screening results should be documented using the appropriate TBI screening code (Table A.2).

Coding at Initial and Subsequent Encounters

The ICD-10-CM coding follows an etiology, location, severity, encounter (ELSE) coding structure to facilitate accurate coding of injuries and encounters (Table A.3) [12].

Coding the Initial Encounter

For TBI encounters, on the initial visit at an MTF for TBI, the reason for which the patient presented, the primary diagnosis code assigned will be the respective ICD-10-CM brain injury (often in the S06.series, with seventh character "A"), followed by a history of TBI unique code assigned during the same encounter (see Sect. 3.X). Any associated/relevant injuries, conditions, or status will also be coded during that encounter [5]. Deployment status will be captured as relevant (e.g., Z56.82 military deployment status). TBI external cause of morbidity code is an important code to be assigned at the initial, diagnosing, and encounter (Box A.1).

Table A.2 TBI screening codes

DoD0121	Screening for traumatic brain injury (TBI), negative findings
DoD0122	Screening for traumatic brain injury (TBI), positive findings
DoD0123	Screening for traumatic brain injury (TBI), declined by patient
DoD0124	Screening for traumatic brain injury (TBI), not performed due to existing diagnosis of TBI
DoD0125	Screening for traumatic brain injury (TBI), not performed due to reason other than existing TBI diagnosis
Z13.850	Encounter for screening for traumatic brain injury (used when documentation is insufficient to determine findings or findings are inconclusive)

Table A.3 ELSE coding structure

S06.311A – Contusion and laceration of the *right* cerebrum with LOC of 30 min or less, initial encounter				
	E – Etiology	L – Location	S – Severity	E – Encounter
S06	3	0	1	A
Intracranial injury	Contusion and laceration of the cerebrum	Right	With LOC of 30 min or less	Initial encounter

Box A.1 Example of Initial Visit for a Newly Diagnosed Concussion: ICD-10-CM

1. S06.0X0A or S06.0X1A (with initial visit seventh character = A)
2. Any specific symptom codes which are addressed by a special procedure, prescription, or test (e.g., code "headache" if medication is prescribed to moderate headache pain)
3. Z56.82 (deployed) or Z91.82 (history of military deployment)
4. DoD0122 (screening for TBI, positive findings) (not required by MHS guidelines)
5. War operations (Y36 with initial visit seventh character = A) or military operations (Y37 with initial visit seventh character = A)
6. DoD unique code for personal history of TBI (e.g., DoD0102 – personal history of TBI, highest level of severity mild)

Coding Subsequent Encounters

MHS guidelines require that subsequent encounters, those occurring for treatment during the healing or recovery phase, are to be assigned the appropriate TBI code with seventh character "D," with the respective DoD unique history of TBI code as a secondary code. If patient at subsequent visit presents with signs of symptoms as a direct result of TBI, indicative of TBI sequela, then the seventh character "S" will be used. During these encounters, the appropriate external cause codes (V-Y codes) should also be assigned (Boxes A.2 and A.3).

Box A.2 Follow-Up Visit for a Diagnosed Concussion with Active Symptoms: ICD-10-CM

1. Any symptoms that are currently present and believed to be related to the concussion
2. S06.0X0D or S06.0X1D (with subsequent/aftercare seventh character = D)
3. Z56.82 (deployed) or Z91.82 (history of military deployment)
4. War operations (Y36 with subsequent/aftercare seventh character = D) or military operations (Y37 with subsequent/aftercare seventh character = D)
5. DoD unique code for personal history of TBI (e.g., DoD0102 – personal history of TBI, highest level of severity mild)

Box A.3 Follow-Up Visit for a Diagnosed Concussion with Resolution of Symptoms: ICD-10-CM

1. S06.0X0D or S06.0X1D (with subsequent/aftercare seventh character = D)
2. Z56.82 (deployed) or Z91.82 (history of military deployment)
3. War operations (Y36 with subsequent/aftercare seventh character = D) or military operations (Y37 with subsequent/aftercare seventh character = D)
4. DoD unique code for personal history of TBI (e.g., DoD0102 – personal history of TBI, highest level of severity mild)

Most individuals with concussion/mTBI have a full recovery without sequela. When there are continued symptoms resulting from the concussion/mTBI, the sequela (e.g., symptom) is coded before the sequela of injury code (e.g., S06. with seventh character "S").

Multiple TBIs

MHS guidelines specify the coding of initial and acute TBI and TBI symptoms, as well as the best practices for subsequent coding of TBI and coding of TBI sequela. For clinical care as well as monitoring and reporting purposes, adherence to coding guidelines is very important. In the

Table A.4 DoD unique history of TBI codes: DoD unique code or ICD-10-CM code

Z87.820	Personal history of TBI, highest level of severity unknown
DoD0101	Personal history of TBI, highest level of severity unknown
DoD0102	Personal history of TBI, highest level of severity *mild* (Glasgow coma scale 13–15), *loss of consciousness <1 h*, post-trauma amnesia <24 h *(Note: this code will be used in FY 2014 only for loss of consciousness of 0–30 min)*
DoD0103	Personal history of TBI, highest level of severity *moderate* (Glasgow coma scale 9–12), *LOC 1–24 h*, post-trauma amnesia 2–7 days *(Note: this code will be used in FY 2014 only for loss of consciousness of >30 min and <24 h)*
DoD0104	Personal history of TBI, highest level of severity *severe* (Glasgow coma scale 3–8), LOC >24 h, post-trauma amnesia >7 days
DoD0105	Personal history of TBI, penetrating intracranial wound (no level of severity assigned)

event that a patient is still in the recovery phase of a previously documented TBI and he or she sustains a new TBI, providers are to apply the initial TBI code, often in the S06.series with seventh character "A," thus recording a new, separate TBI (i.e., S06.0X0A). Subsequent encounters for treatment during the healing or recovery phase are assigned an ICD-10-CM TBI coding with a seventh character ending of "D" (i.e., S06.0X0D).

History of Traumatic Brain Injury

Due to the utility of unique DoD history of TBI codes for tracking and reporting of TBI, these codes are used during the active and healing/recovery phases of treatment, in addition to serving as personal history codes. Of note, according to MHS guidelines, history of TBI codes is not to be assigned to patient encounters not resulting in a TBI diagnosis, regardless of setting (inpatient or outpatient). Only initial "A," subsequent "D," or sequela "S" visits with an ICD-10-CM TBI code assigned can be accompanied by a DoD unique history of TBI codes (DoD0101- DoD0105).

For patients with a history of multiple TBIs, providers will use only the history of TBI code for the highest level of TBI. Within the MHS, DoD unique history of TBI codes (DoD0101-DoD0105) will be used instead of the Z87.820 used in the civilian sector and by MHS network providers (personal history of TBI) (Table A.4).

Additionally, in the MHS, although penetrating TBI is indicative of mechanism of injury, a penetrating intracranial wound is considered a TBI of a higher severity level than severe TBI. Therefore, the code for a penetrating injury will be used as the basis of recording the TBI severity of that patient, namely, DoD0105 (personal history of TBI, penetrating intracranial wound).

TBI Symptom, External Cause of Injury, and Deployment Coding

Symptoms and Sequela

TBI is often accompanied by a number of symptoms. They include physical symptoms such as headache, fatigue, balance issues, and sensory symptoms, such as blurred vision or light sensitivity. Cognitive and emotional/behavioral symptoms may include memory or concentration issues or feelings of anxiety or depression, respectively. The ICD-10-CM codes for most commonly associated symptoms are presented (Table A.5) [12].

TBI External Cause of Injury Codes

Coding of the external cause of injury is crucial to clinical care, monitoring, and reporting as well as preventive efforts. External causes of injury codes often associated with TBI include falls (W00-W19), motor vehicle accidents (V40-V49), striking against or being struck (V20-V49), assault (X92-Y09), operations of war (Y36), and military operations (Y37). Oftentimes, the seventh character will be "A," indicating an initial encounter for this

Table A.5 TBI symptom codes

ICD-10-CM	Definition
Memory symptoms	
R41.1/2/3	Anterograde amnesia, retrograde amnesia, other amnesia
Cognitive/language processing symptoms	
R41.82	Altered mental status, unspecified
R41.840/1/2/4	Attention and concentration deficit/cognitive communication deficit/visuospatial deficit/frontal lobe and executive function deficit
R41.89	Other symptoms and signs involving cognitive functions and awareness
R41.9	Unspecified symptoms and signs involving cognitive functions and awareness
R47.01	Aphasia
I69.91	Cognitive deficit
Hearing symptoms	
H90.2	Conductive hearing loss, unspecified
H90.5	Unspecified sensorineural hearing loss
H90.8	Mixed conductive and sensorineural hearing loss, unspecified
H91.90/91/92/93	Unspecified hearing loss, unspecified ear/right ear/left ear/bilateral
H93.231/2/3/9	Hyperacusis, right ear/left ear/bilateral/unspecified ear
H93.11/2/3/9	Tinnitus, right ear/left ear/bilateral/unspecified ear
Headache and other neurologic symptoms	
H81.41/2/3/9	Vertigo of central origin, right ear/left ear/bilateral/unspecified ear
H81.8X1/2/3/4	Other disorders of vestibular function, right ear/left ear/bilateral/unspecified ear
G43.001/9	Migraine without aura, not intractable, with status migrainosus/without status migrainosus
G43.101/9	Migraine with aura, not intractable with status migrainosus/without status migrainosus
G43.701	Chronic migraine without aura, not intractable, with status migrainosus
G43.901/9	Migraine, unspecified, not intractable, with status migrainosus/migraine, unspecified, not intractable, without status migrainosus
G44.209	Tension-type headache, unspecified, not intractable
G44.1	Vascular headache, not elsewhere classified
G44.321/9	Chronic post-traumatic headache, intractable/chronic post-traumatic headache, not intractable
G44.301/9	Post-traumatic headache, unspecified, intractable/post-traumatic headache, unspecified, not intractable
G44.311 / 9	Acute post-traumatic headache, intractable/acute post-traumatic headache, not intractable
R43.0	Anosmia – disturbances of sensation of smell and taste
Emotional/behavioral symptoms	
F10.10	Alcohol abuse, uncomplicated
F32.9	Major depressive disorder, single episode, unspecified
F41.1/9	Generalized anxiety disorder/anxiety disorder, unspecified
F43.0	Acute stress reaction, unspecified
R11.0	Nausea
R45.0/1/3/4/5	Nervousness/restlessness, agitation/demoralization, apathy/irritability, and anger/hostility
R45.86/7/9	Emotional lability/impulsiveness/other signs and symptoms involving emotional state
R46.2	Strange and inexplicable behavior
R53.1/81/83	Weakness/other malaise/other fatigue
Sleep symptoms	
G47.00/01/09/30/33	Insomnia, unspecified/insomnia due to medical condition/sleep apnea, unspecified/other organic insomnia
R06.81	Apnea, not elsewhere classified
G47.20	Circadian rhythm sleep disorder, unspecified type
Vision symptoms	
H52.7	Unspecified disorder of refraction
H53.149	Visual discomfort, unspecified
H53.2/4/8	Diplopia/heteronymous bilateral field defects/other visual disturbances

external cause of injury; for other visits, use the appropriate seventh character (D, subsequent/follow-up encounters, or S, sequela).

Deployment Status

The deployment status of a military member may be particularly relevant to the diagnosis of mTBI, such as when an injury is sustained or being treated in combat. Similarly, if a patient is being treated for an mTBI that was sustained in a deployed setting, but is still not resolved, that information should be documented. There are two codes most often used in these circumstances: Z56.82 (military deployment status) to be used while deployed and Z91.82 (personal history of military deployment) used to associate an injury to a deployment when being treated for a noncombat injury.

Pre-existing Conditions

Pre-existing conditions, such as migraines (G43.4X), major depressive disorders (F32X, F33X), post-traumatic stress disorder (F43.1X), and substance use disorder (F10X-F19X) which impact care, are often coded during a TBI patient's encounter. Given that pre-existing conditions may have symptoms similar to TBI and may complicate resolution of TBI-related issues, their documentation is important.

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