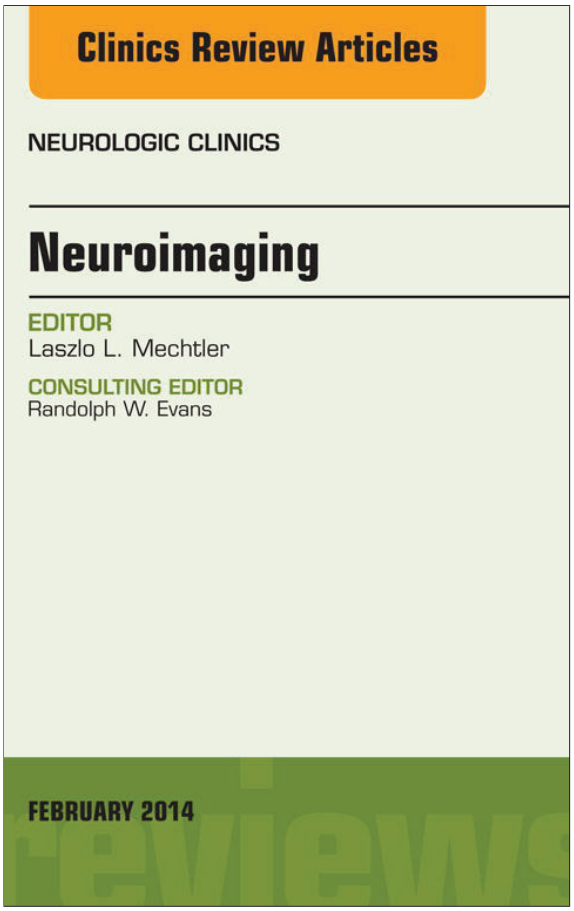

Advanced Neuroimaging of Mild Traumatic Brain Injury

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KEYWORDS

- Mild traumatic brain injury • Concussion • Diffuse axonal injury
- Diffusion tensor imaging • Susceptibility-weighted imaging
- Magnetic resonance spectroscopy

KEY POINTS

- Traumatic brain injury (TBI) is an important cause of death and disability in the United States, with annual incidence of approximately 1.7 million and overall annual costs estimated to be $76.5 billion.
- 75% of all TBIs can be classified as mild TBI (mTBI), defined as Glasgow Coma Scale score of 13 or more. Concussion, a term commonly used in sports-related injuries, is a form of mTBI.
- The goals of neuroimaging in TBI are to identify treatable injuries, assist in the prevention of secondary damage, and provide useful prognostic information on a patient's long-term clinical condition.
- Advanced neuroimaging of mTBI includes anatomic/structural imaging techniques, such as diffusion tensor imaging and susceptibility-weighted imaging, and functional imaging techniques such as functional MRI, perfusion-weighted imaging, MR spectroscopy, and positron emission tomography.

INTRODUCTION

Traumatic brain injury (TBI), a major public health concern at the beginning of the 21st century, has been called a "silent epidemic"[1] because it is underreported, often remains undiagnosed, and its long-term consequences are generally underrecognized. However, owing to growing experience with combat-related TBI among military personnel, media focus on TBI-related long-term disability in professional athletes,

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educational initiatives, such as the "Heads Up" program of the Centers for Disease Control and Prevention,[2] and the voices of patients and affected families, the silence is beginning to be broken.

Approximately 75% of all reported TBIs can be classified as mild TBI (mTBI).[3] Although most patients with mTBI become asymptomatic within days to weeks, some develop persistent troubling symptoms that have been referred to as "persistent postconcussive syndrome."[4,5] One of the inherent challenges in applying neuroimaging to predict clinical outcome in mTBI is that patients who develop persistent symptoms typically have no detectable abnormalities on conventional neuroimaging, such as computed tomography (CT) and magnetic resonance imaging (MRI) of the brain. Novel structural and functional neuroimaging techniques have emerged that have the sensitivity to identify hitherto undetected brain abnormalities in mTBI. This article focuses on advancements in neuroimaging techniques, compares the advantages of each of the modalities in the evaluation of mTBI, and discusses their contribution to our understanding of the pathophysiology as it relates to prognosis.

MTBI: BRIEF OVERVIEW

Terminology

"Traumatic brain injury" refers to an alteration in brain function or other evidence of brain pathology caused by external force[6] and traditionally is classified as mild, moderate, and severe based on the Glasgow Coma Scale (GCS).[7] TBI with GCS score of 13 or more is classified as mild, 9 to 12 as moderate, and 8 and lower as severe.[8] mTBI is defined as a traumatically induced physiologic disruption of brain function as manifested by at least 1 of the following: (1) any period of loss of consciousness up to 30 minutes, (2) any loss of memory for events before or after the accident not exceeding 24 hours, (3) any alteration in mental state at the time of the accident, and (4) focal neurologic deficits that may or may not be transient.[9,10] Concussion is a form of mTBI, and "concussion" is a term commonly used in sports, whereas "mTBI" is used more often in the medical context.[11]

Pathophysiology

Pathophysiologically, TBI involves 2 phases of tissue injury: primary and secondary. Whereas primary injuries are almost immediate and generally irreversible, secondary injuries are delayed and can continue for an extended period of time and thereby provide an opportunity for therapy.[12] The primary injury phase involves direct and indirect mechanical damage from impact and acceleration/deceleration that could result in cortical contusions, subdural or epidural hematomas, axonal shearing, and microvascular injury. Secondary injury is the nonmechanical damage that results from a complex metabolic cascade set off by neuronal cell membrane disruption and axonal stretch.[13] Neuronal membrane deformity leads to ionic flux and release of excitatory neurotransmitters. Attempts to restore homeostasis lead to a cellular energy crisis. Depletion of cellular energy stores leads to initiation of apoptosis and neuronal death. Impaired cerebrovascular autoregulation that leads to decreased cerebral blood flow (CBF), inflammatory response with activation of microglia,[14] and release of free radicals are additional mechanisms of tissue damage during the secondary injury phase of TBI.

Diffuse axonal injury (DAI) is best described after severe TBI and is characterized by axonal stretching leading to axolemmal disruption, ionic flux, neurofilament compaction, and microtubule disassembly. The effect of these pathophysiologic processes is axonal swelling and eventual disconnection.[15,16] Although best described in severe TBI, DAI occurs in mTBI as well and is recognized as an important determinant of

long-term cognitive and neuropsychiatric outcome in mTBI.[17,18] As discussed in subsequent sections, key advances in neuroimaging of mTBI involve newer techniques that can detect disruption of axonal integrity.

Symptomatology

mTBI can lead to a wide range of symptoms, including loss of consciousness, if any, at the time of injury and memory loss, if any, for events before and after the injury. Postconcussion syndrome refers to symptoms from multiple "symptom categories" that develop within a maximum of 4 weeks following head trauma.[19] Broad symptom categories include somatic, cognitive, affective, and sleep-related. Typical symptoms include headache, dizziness, memory impairment, difficulty concentrating, insomnia, mood alteration, and anxiety. Most people with mTBI recover within a few days to weeks with rest and minimal symptomatic treatment. Approximately 15% of patients with mTBI suffer from long-term complications.[4,5]

Chronic traumatic encephalopathy (CTE) is a rare progressive degenerative condition that is thought to be a consequence of repetitive TBI. First described as *dementia pugilistica* in boxers,[20] CTE is equally concerning for other professional athletes who are at risk for repeated concussions. For instance, retired professional football players with history of 3 or more concussions are 5 times more likely to develop mild cognitive impairment.[21] From the autopsy studies of 3 professional athletes with CTE, we know that it is related to deposition of tau protein in neurons and resultant progressive degeneration of the central nervous system.[22]

CONVENTIONAL NEUROIMAGING OF TRAUMATIC BRAIN INJURY

General Considerations

The goals of neuroimaging of TBI are to identify treatable injuries, assist in prevention of secondary damage, and provide prognostic information about long-term clinical outcome. Conventional neuroimaging continues to play a crucial role in the initial management of TBI. CT is generally the imaging modality of choice for initial screening to exclude serious intracranial injury in patients who present with head injury. MRI, particularly at 3 T strength, improves structural sensitivity and is indicated in acute TBI when neurologic findings cannot be explained by CT. MRI is also recommended for evaluation of TBI-related symptoms in the subacute and chronic phases of injury.[23]

Standard questions in this area are as follows: which patients with TBI should be imaged, when, and how? The general consensus is that moderate and severe TBI should be imaged with CT immediately.[24] At present, consensus is lacking regarding the imaging of mTBI. Various guidelines that address the use of CT for initial assessment of TBI have been proposed, including the National Institute of Health and Clinical Excellence guidelines in the United Kingdom,[25] the Canadian CT Head Rule,[26] the American College of Emergency Physicians clinical policy,[27] and the New Orleans Criteria.[28] Some of these guidelines have been validated.[29,30] Overall, implementation of the guidelines in emergency departments (EDs) has proven to be cost effective, owing primarily to a decrease in hospital admission rates. However, an estimated 10% to 35% of CT scans obtained in EDs for mTBI (GCS$\geq$13) are not compliant with the guidelines.[31]

In 2012, the American College of Radiology published revised appropriateness criteria for imaging in head trauma.[32] In cases of minor or mild acute closed-head injury (GCS$\geq$13) without risk factors or neurologic deficits, the study of choice is CT of the head without contrast, despite its low yield. Among patients who present to EDs with GCS scores of 15, 6% to 7% have positive findings on head CT scans.

The rates of intracranial abnormalities and subsequent neurosurgical intervention are higher in pediatric patients.[33,34] In moderate TBI (GCS 9–12), the incidence of CT abnormalities is approximately 61%.[35]

CT

In patients with head injury, CT can help to detect intracranial hemorrhage, mass effect, midline shift, ventricular distortion, skull fractures, displaced bone fragments, foreign bodies, and intracranial air. CT scans offer several advantages: scanner-equipped facilities are widely available, they generally offer convenient hours of operation,[36] and scanning is extremely fast, typically requiring only a few seconds to obtain a head CT. Faster scan times minimize the risk of image degradation from motion artifact, which could be a significant concern, for instance, in the disoriented patient or a young child. Multidetector CT scanners have multiple rows of detectors (eg, 16, 64, 128, 256, 320 "slices") that permit greater coverage per rotation, high resolution, and faster scanning times. Slices degraded by motion artifact can easily be repeated. A 320-slice CT scanner can image a 16-cm (6.3-inch) volume in less than 1 second. Scan times on the higher-slice CT scanners can actually reduce radiation dose, which is very advantageous, especially in the pediatric population. CT datasets can be post-processed to yield 2-dimensional (2D) or 3-dimensional (3D) reformatted images (**Fig. 1**). 2D-reformatted images in either the coronal or sagittal plane in addition to the axial plane have become a standard in many EDs.

Following neurologic deterioration, patients with closed-head injuries should undergo repeat head CT with clinical neurologic assessment to determine if a surgically

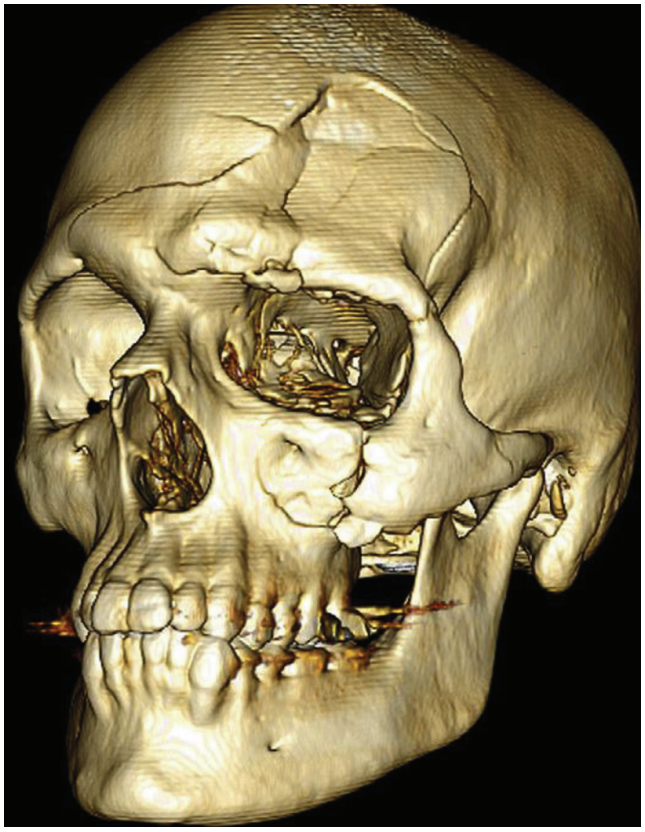

Fig. 1. Depressed frontal fracture: 3D surface-rendered images of the skull and face are useful for depicting displaced fractures before repair. (*From* Kubal WS. Updated imaging of traumatic brain injury. Radiol Clin North Am 2012;50(1):15–41; with permission.)

correctable lesion is present, as is the case in more than one-third of patients. Scheduling repeat head CTs within 24 hours for patients with mild head injury is a standard practice in many trauma centers. However, recent studies have shown that it is unnecessary to routinely schedule repeat CT scans when patients are unchanged or improving neurologically.[37–39]

CT angiography (CTA) has a role in the diagnosis and management of traumatic vascular injury, such as pseudoaneurysm, dissection, or uncontrolled hemorrhage. Vascular injuries typically occur with penetrating trauma, skull base fractures, or neck trauma. In these cases, CTA is best performed with a multidetector scanner and a rapid bolus of contrast injection using vessel tracking.[40] Although conventional angiography remains the gold standard for detecting arterial dissections, carotid or vertebral dissections can be detected by CTA of the aortic arch and neck. Independent predictors of arterial injury in blunt trauma include cervical facet subluxation or dislocation, fracture lines approaching an artery, and high-impact injury mechanisms.[41]

CT Overuse and Radiation Exposure

The number of CT scans performed annually in the United States has markedly increased, rising from 3 million in 1980 to 20 million in 1995 and to more than 60 million in 2005.[42] Studies show that in excess of 30% of patients had more than 3 CT examinations, 7% had more than 5 examinations, and 4% had more than 9 examinations,[43] and that between 10% and 35% of CTs obtained in EDs for minor or mild head injury are not guideline compliant.[31] An obvious consequence of overuse of CT scanning is excessive health care expenditure. It is believed that ensuring strict compliance with published guidelines could potentially save $394 million annually.

The other major concern related to CT overuse is radiation exposure and risk of cancer. Up to 2% of all cancers in the United States may be attributable to radiation from CT.[42] The typical radiation dose for head CT is 3 mSv. The risk of cancer associated with this ionizing radiation dose is age and gender dependent, but it is approximately in the order of magnitude of 1 radiation-induced cancer per 10,000 CTs performed in adult patients.[44] The lifetime risk of mortality from leukemia or solid-organ malignancy from a single pediatric head CT ranges from approximately 1:2000 for infants to 1:5000 for older children.[45] Certain characteristics render the pediatric population particularly susceptible to the harmful effects of ionizing radiation. Children have rapidly dividing cells that are more sensitive to the effect of radiation. Compared with an equivalent dose in an adult, radiation exposure in a child is associated with a 10-fold increase in neoplastic potential.[46] In addition, children have a longer lifetime during which radiation-related cancers can develop. Finally, until the past few years, most CT scans were not performed with due consideration to the smaller size of children, resulting in children receiving a higher relative radiation dose than did adults.[47] The acronym ALARA (as low as reasonably achievable) highlights an important principle in radiation safety that is also a regulatory requirement, that of minimizing the radiation exposure by using all reasonable measures.[48] Measures that help to reduce the radiation dose associated with CT are listed in **Box 1**.

Overuse of health care resources can be largely attributed to the practice of defensive medicine, whereby tests or services of marginal or no medical value are ordered out of fear of litigation. CT imaging rates for head injury are lowest in EDs in those states that have passed tort reform laws.[44] Ultimately, the decision to perform a CT scan for a minor or mild head injury is a clinical decision based on weighing the risk of serious underlying intracranial injury or skull fracture against the risk of harm from radiation exposure.[49]

Box 1
Reasonable measures for reduction of radiation exposure associated with CT

- Appropriately justify CT examinations for clinical need
- Develop weight-based protocols
- Improve shielding
- Perform focused and/or limited-view studies when clinically appropriate
- Avoid "routine" repeat CT studies
- Consider alternative nonradiation modalities, such as ultrasound or MRI

MRI

MRI has better resolution and can detect structural abnormalities earlier than did CT. However, historically, MRI use in the assessment of head trauma has been hindered by its limited availability in the acute trauma setting and EDs, longer scan times, sensitivity to patient motion, and relative insensitivity to subarachnoid hemorrhage. Other factors include need for MRI-compatible monitoring equipment and ventilators, contraindications (such as most cardiac pacemakers and some cerebral aneurysm clips), and risk of occult foreign bodies.

Over time, many of these limitations have been addressed, and technological advancements have made this imaging modality more readily available and quite popular in the acute trauma setting. Advances such as open-bore geometry, rapid-scan sequences, motion-correction algorithms, and improved patient-monitoring equipment have allowed a greater role for MRI in closed-head injury. MRI is particularly valuable in the assessment of pathology in the brainstem, posterior fossa, and brain parenchyma adjacent to the calvaria.[50] As mentioned previously, it is also the imaging modality of choice when neurologic findings in patients with acute TBI cannot be explained by CT, and it is the recommended modality for evaluation of TBI-related symptoms in the subacute or chronic phase of injury.[23,50]

Structural MRI in mTBI

Standard T1-weighted imaging provides excellent resolution of the more striking anatomic findings in TBI, such as mass effect, midline shift, and ventricular distortion. The addition of gadolinium-based contrast offers no significant advantage for lesion detection or characterization when compared with noncontrast MRI in patients with head injury. More subtle structural abnormalities in mTBI are best seen with key MRI sequences, such as gradient-recalled echo (GRE) for hemorrhagic DAI and contusions, and fluid-attenuated inversion-recovery (FLAIR) for nonhemorrhagic DAI and subarachnoid hemorrhage.

Routine GRE images are sensitive to the presence of blood breakdown products, including deoxyhemoglobin, intracellular (but not extracellular) methemoglobin, ferritin, and hemosiderin. In GRE pulse sequences, the 180° refocusing pulse is omitted and a flip angle smaller than 90° is used, thereby significantly reducing scan time. Echo-planar imaging uses rapid gradient switching instead of repeated radiofrequency excitations, resulting in much shorter scan times than those of conventional GRE.

FLAIR produces T2-weighted images with attenuated cerebrospinal fluid signal by using an inversion prepulse placed at the cerebral spinal fluid null point, followed by a long echo time readout. As a result, periventricular and cerebral cortical lesions

become more conspicuous. Compared with conventional T2-weighted images, FLAIR is far superior in its sensitivity for cortical contusions, DAI, and subarachnoid hemorrhage.[51]

Short tau (or TI) inversion recovery (STIR) uses an inversion prepulse that selectively suppresses the fat signal and improves long-T1/long-T2 lesion conspicuity. It is particularly useful in avoiding chemical shift artifacts[52] and is commonly used to differentiate lipomas from hemorrhage and, in the setting of trauma, for the evaluation of optic nerve injury and vertebral body compression fractures. However, its usefulness in TBI is somewhat limited. STIR should not be used to evaluate for gadolinium-contrast enhancement, as the short tau of gadolinium will also be suppressed by the inversion prepulse. Chemical, fat-suppressed, T1-weighted images are preferable for the evaluation of contrast enhancement when fat suppression is desired, such as in the orbits.

Magnetization transfer imaging (MTI) uses off-resonance prepulses that reduce signal from semisolid tissue, such as brain parenchyma, relative to the signal from more fluid tissue, such as blood. Typically, MTI has been shown to be sensitive in the detection of white matter abnormalities in such disorders as multiple sclerosis, progressive multifocal leukoencephalopathy, and wallerian degeneration.[53] Magnetization-transfer ratio provides a quantitative measure of the structural integrity of tissue. Studies have shown that a reduction of magnetization-transfer ratio correlates with worse clinical outcome in patients with TBI.[54,55]

ADVANCED STRUCTURAL NEUROIMAGING OF MTBI

DAI occurs in both direct- and indirect-impact TBI and is the most common cause of long-term disability and functional deficits in patients. Even mTBI can be associated with significant DAI. Hemorrhagic and nonhemorrhagic shearing lesions are located in the major white matter tracts, spreading from the surface to deeper structures, such as corpus callosum, internal capsule, and brainstem. Conventional neuroimaging is insensitive to DAI.[56]

Susceptibility-Weighted Imaging

One of the key advancements in the imaging of mTBI has been susceptibility-weighted imaging (SWI), which is a technique that exploits differences in magnetic susceptibility between tissues. The particular advantage that SWI confers is detection of microhemorrhages that are not seen on conventional MRI (**Fig. 2**). In the setting of TBI, microhemorrhages are thought to be neuroimaging markers of hemorrhagic DAI. SWI is up to 3 to 6 times more sensitive than is GRE in detecting hemorrhagic DAI.[57] SWI is also very sensitive for hemorrhagic DAI in the cerebellum and brainstem.

Detection of microhemorrhages depends on a number of factors, including pulse sequence, echo time, slice thickness, spatial resolution, and, possibly, imaging plane.[58] SWI is best obtained at higher field strengths, as the echo time is much longer in low fields and acquisitions need to be longer at higher field strengths.[59] The signal-to-noise ratio is also higher. With the advent of parallel imaging and the greater availability of clinical 3-T scanners, it is now possible to image the entire brain with SWI in approximately 4 minutes.[60]

In a study of TBI in the pediatric population,[61] SWI lesions were detected in children at all injury severity levels, indicating that the technique can be useful not only for diffuse/severe axonal injuries, but also for identification of mild and focal injuries. Nineteen percent of patients with mTBI who had either not undergone a clinical CT or had negative CT findings were found to have SWI lesions. Most injuries were located in the

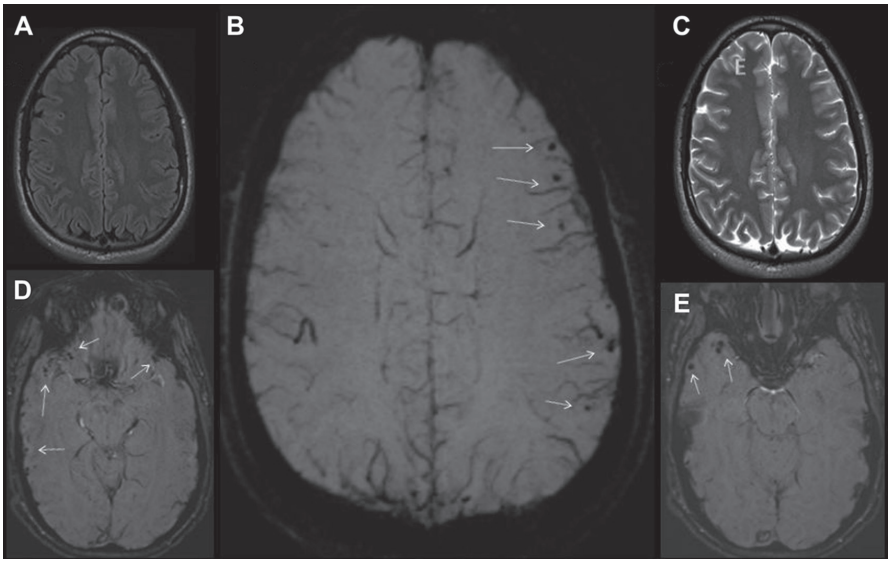

Fig. 2. A 14-year-old teenager with mTBI and postconcussive symptoms secondary to a bicycle accident. (*A*) FLAIR and (*C*) T2-weighted images were unremarkable. (*B, D, E*) SWI images show microhemorrhages (*arrows*) in juxtacortical locations and in orbitofrontal and temporal lobes.

frontal lobes, often in combination with lesions in the temporal, parietal, and occipital lobes. The study found that the greater the number of SWI lesions, the worse the intellectual functioning. This finding is indicative of an association between SWI lesions and intellectual functioning that can be detected as early as 6 months after injury.[61–63] SWI has detected microhemorrhages in amateur boxers that were not detected with T2 fast spin echo or T2* GRE sequences.[64] Although CT may be important for early classification of brain injury, MRI in combination with SWI is superior for accurate diagnosis and assessment of need for neurosurgery. SWI can play an important role in accurately diagnosing the degree of injury and in determining the aggressiveness of management and rehabilitation.

Diffusion-Weighted Imaging

Mobility of water molecules is the essential contrast mechanism exploited in diffusion-weighted imaging (DWI), reflecting a measure of the apparent diffusion coefficient (ADC). Areas with a high degree of diffusion, such as the cerebrospinal fluid, will be hypointense on DWI and display a high ADC value. Areas with restricted diffusion (eg, protons within the gray and white matter) will be hyperintense on DWI and display a low ADC value. This technique allows differentiation between cytotoxic edema (restricted diffusion) and vasogenic edema (increased diffusion). Focal areas of restricted diffusion are often seen in patients with TBI and have been associated with DAI or cerebral edema. Acute DAI lesions appear bright on DWI and dark on ADC because of restricted diffusion from acute cell death. DWI reveals a greater extent and degree of abnormality than do T2-weighted and FLAIR images, and the measured ADC values of the white matter are lower in patients with more severe injuries.[65] Decreased ADC can be demonstrated in the acute phase of DAI and may persist into the subacute phase for a period of time beyond that described for cytotoxic edema. Mean ADC in the whole brain is the best predictor of outcome among all degrees of TBI.[66] Lower ADC scores were found to be predictive of the duration of coma or functional outcome in patients with severe TBI. DWI may be especially useful in assessing nonaccidental injury in children.[67]

Diffusion Tensor Imaging

An extension of the DWI technique is diffusion tensor imaging (DTI), in which diffusion data are acquired in 6 or more directions. A tensor is used to describe diffusion in an anisotropic system. DTI allows visualization of the location, orientation, and anisotropy of the brain's white matter tracts. A fractional anisotropy (FA) value of zero means that the diffusion is isotropic (ie, free diffusion in all directions), whereas an FA value of 1 indicates that diffusion occurs only along one axis and is fully restricted along all other directions. Color coding the various axonal projections in a 2D representation produces a color FA map. The standard convention for color coding the FA map is that green represents anterior-posterior pathways, red represents commissural (lateral) pathways, and blue represents cranial-caudal (ascending and descending) pathways. A 3D representation is referred to as diffusion tractography (eg, **Fig. 3**).[68]

Three major approaches are used to examine microstructure damage from DTI data: (1) whole-brain voxel-based analysis, (2) region-of-interest analysis, and (3) in vivo tractography.[69,70] Briefly, whole-brain voxel-based DTI analysis is an operator-independent approach that allows the analysis of entire brain volume. Another approach consists of finding a region of interest to identify between-group differences and correlations in a specific brain region. DTI also provides opportunity to perform in vivo tractography, or virtual dissections, of major white matter pathways.

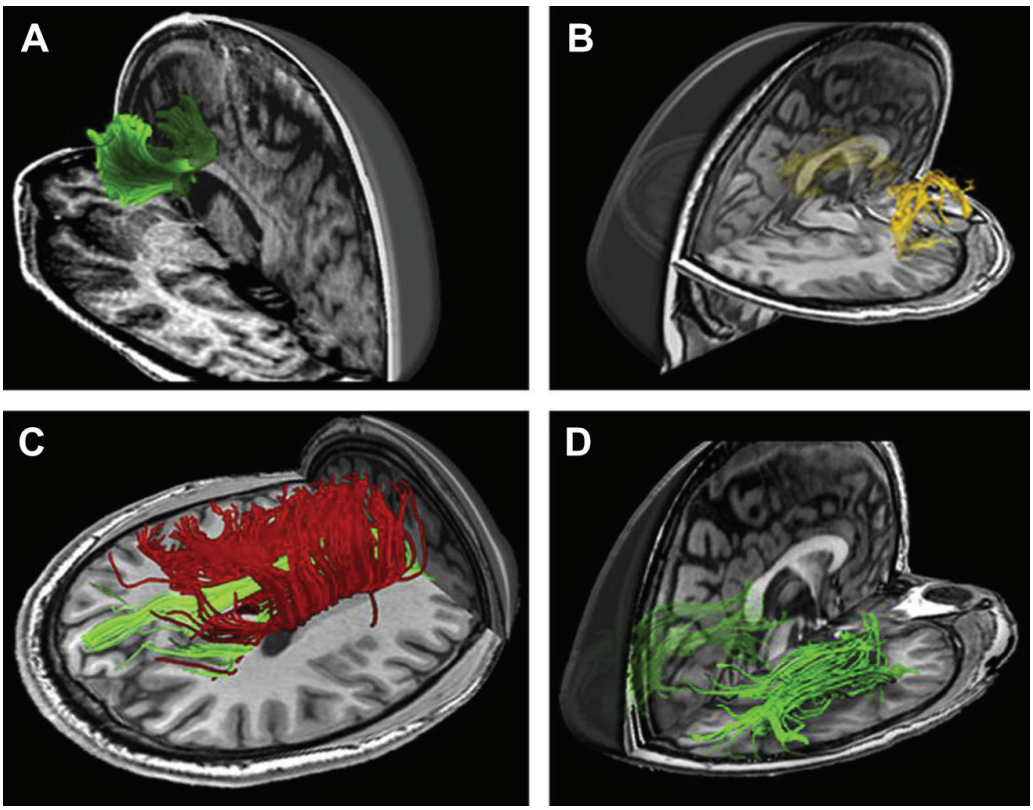

Fig. 3. Fiber tractography of commonly damaged tracts in mTBI: (*A*) anterior corona radiata and genu of corpus callosum, (*B*) uncinate fasciculus, (*C*) cingulum bundle in green and body of corpus callosum in red, and (*D*) inferior longitudinal fasciculus. (*From* Niogi SN, Mukherjee P. Diffusion tensor imaging of mild traumatic brain injury. J Head Trauma Rehabil 2010;25(4):241–55; with permission.)

Over the past decade, the literature has grown significantly regarding the use of DTI in mTBI. Cases have been reported of mTBI with normal CT and GCS score of 15 in adolescents who were found to have increased FA and decreased diffusivity in the corpus callosum within 6 days after injury.[71] Cognitive, affective, and somatic post-concussion symptoms were all related to DTI indices of corpus callosum integrity, including FA. Furthermore, DTI measures of white matter fiber tract integrity were assessed in varsity-level college athletes who had sports-related concussion without loss of consciousness and experienced symptoms for at least 1 month after injury.[72] Notable abnormalities in structural integrity were present in subjects after they sustained concussion. The structures most affected were the left temporal lobe, the retrolenticular part of the internal capsule, and the posterior thalamic radiation, which contains fibers that connect the frontal and occipital lobes as well as the temporal and occipital lobes. Affected patients were found to have increased mean diffusivity and decreased FA compared with controls.

Two major patterns of DTI changes have emerged in mTBI. Decreased FA or increased mean diffusivity in patients with mTBI compared with age-matched healthy controls has been shown, indicating loss of directional diffusivity or anisotropy, suggesting microstructural disruption of white matter.[73,74] Other studies have demonstrated seemingly contradictory increases in FA in patients with mTBI compared with controls.[71,75] However, these patients were, in general, imaged sooner after injury than those in the comparative studies. Unlike the previously mentioned studies, the investigators suggested that increases in FA may be caused by acute axonal injury

that results in overall reduction and diffusivity akin to cytotoxic edema. Decreased FA in mTBI may represent chronic structural injuries and correlate with postconcussion symptoms. DTI images from 72 veterans of the Iraq and Afghanistan wars who had mTBI were compared with DTI images from 21 veterans with no TBI during deployment.[76] Several years after the trauma, veterans with a history of mTBI had a higher number of diffusely distributed areas of decreased FA (potholes) than did the veterans without history of TBI. DTI abnormalities of the corpus callosum have been consistently associated with decreased cognitive function in TBI. Potholes were also observed in patients who experienced mTBI in civilian settings and were examined within 90 days after the trauma. White matter potholes may constitute a sensitive biomarker of axonal injury that can be identified in mTBI at acute and chronic stages of its clinical course. DTI holds promise as a method by which to objectively assess abnormal cerebral connectivity underlying cognitive deficits in mTBI.

Voxel-based Morphometry

Voxel-based morphometry (VBM) is a method of voxel-by-voxel analysis of 3D MRI data. It is a statistical method that compares regional differences in the concentration of gray matter between 2 groups of individuals. VBM has traditionally been used to assess brain atrophy in Alzheimer disease. This method uses high-resolution images that are spatially normalized into the same stereotactic space. Gray matter is segmented and smoothed, and statistical parametric tests are used to assess differences in gray matter between groups.[77,78] Whole-brain atrophy can be evident 11 months after trauma.[79] It has also been found that all patients with TBI show decreased gray matter concentration in the frontal and temporal cortices, subcortical gray matter, cingulate gyrus, and the cerebellum.[77] The reported gray matter atrophy may have 2 potential mechanisms, one of which could be cortical involvement, as the brain strikes the cranial vault in a coup-contrecoup manner. Next, DAI can cause axonal damage, leading to retrograde degeneration and neuronal somatic loss.[80] The use of VBM in TBI is unique among brain disorders in that the exact time of onset of injury is known. For this reason, longitudinal studies of MRI brain volume in mTBI are more important than cross-sectional analyses. In comparison with a cross-sectional design, a longitudinal study design may be preferable for understanding the progression of brain atrophy after injury and understanding its association with important clinical variables.[81] A recent study demonstrated, via automated volumetric analysis, whole-brain longitudinal changes in global and regional volume in patients 1 year after mTBI. These changes specifically affected the anterior part of the cingulate white matter bilaterally, the left cingulate gyrus isthmus white matter, and the precuneal gray matter.[82]

ADVANCED FUNCTIONAL NEUROIMAGING OF MTBI

Magnetic Resonance Spectroscopy

Magnetic resonance spectroscopy (MRS) is a powerful noninvasive imaging technique that can provide information about metabolic alterations in patients with mTBI, including and especially in the absence of obvious injury on conventional neuroimaging. The most common brain metabolites measured using proton MRS include N-acetyl aspartate (NAA), creatine (Cr), choline (Cho), glutamate/glutamine (Glx), lactate (Lac), and myoinositol (Ins).[83,84] The ability to quantify neuronal and glial metabolites makes MRS a particularly useful tool for repeated studies in survivors of TBI. Higher-field-strength MRI has increased the ability to accurately determine concentrations of a broader range of metabolites, including neurotransmitters like

gamma-amino butyric acid (GABA) and glycine. Very briefly, NAA is synthesized in mitochondria and is a marker in neuronal integrity, Cr is involved in cellular energy metabolism and is assumed to be more or less constant, Cho is a marker of a membrane turnover, Ins is found in glial cells, Glx are excitatory neurotransmitters, and Lac is a marker of anaerobic metabolism and, indirectly, ischemia and hypoxia. The common neurometabolite alterations in mTBI that can be measured using MRS are summarized in **Table 1**.

An extensive body of research indicates that NAA levels (eg, **Fig. 4**) and NAA/Cr ratios are reduced in TBI as a result of neuronal loss and/or dysfunction.[85] Reduced NAA levels have been shown to be predictive of long-term functional outcomes in TBI. Twelve intercollegiate varsity athletes who had sustained sports-related concussions were compared with healthy age-matched controls within 6 days of injury. The NAA/Cr levels were significantly reduced in the primary motor cortex and, to a lesser extent, in the dorsolateral prefrontal cortex in the concussed athletes.[86] Sports-related concussion was the primary focus in another study of 14 individuals in whom MRS was obtained at 3 to 4 days, 15 days, and 30 days after injury. Decreased NAA/Cr ratio was observed at 3 to 4 days following concussion, modest recovery was seen at 15 days postinjury, and normalization of the NAA/Cr ratio was noted by 30 days postinjury. It is of interest that these athletes reported resolution of postconcussive symptoms by day 3, despite abnormal MRS findings.[87] These studies suggest that quantification of neurochemicals with MRS could offer a noninvasive and safe approach to assessing brain cellular injury and response.[88]

Functional MRI

Functional MRI (fMRI) allows assessment of brain function in a noninvasive manner. Neuronal function is inferred from a blood oxygen level–dependent (BOLD) signal that reflects magnetic field inhomogeneity brought about by changes in the oxygenation state of hemoglobin. Neuronal activation results in a local increase in CBF in the area out of proportion to the cerebral oxygen consumption, thereby resulting in net reduction in the amount of deoxyhemoglobin. As neuronal activity increases, blood flow overcompensates such that the local blood oxygenation actually increases. Because deoxyhemoglobin is an endogenous paramagnetic contrast agent, a decrease in its concentration is reflected as an increase in BOLD signal. fMRI can be performed at either 1.5 T or 3.0 T, but higher field strength is generally preferred. To accentuate the differences, this test is usually performed while the patient completes a neurocognitive task, which places an increased demand on the brain, and differences in local perfusion are measured in real time.[89] fMRI holds great potential for

Table 1
Common neurometabolite alterations in mTBI

Neurometabolite	Role in/Marker of	Alteration in TBI
NAA	Neuronal/axonal integrity	Reduced
Cr	Cellular energy metabolism	Constant
Cho	Membrane synthesis/repair	Increased
Lac	Anaerobic glycolysis	Increased
Glx	Excitatory neurotransmitters	Increased
Ins	Inflammation (glial cells)	Increased

Abbreviations: Cho, choline; Cr, creatine; Glx, glutamate/glutamine; Ins, myoinositol; Lac, lactate; mTBI, mild traumatic brain injury; NAA, N-acetyl aspartate; TBI, traumatic brain injury.

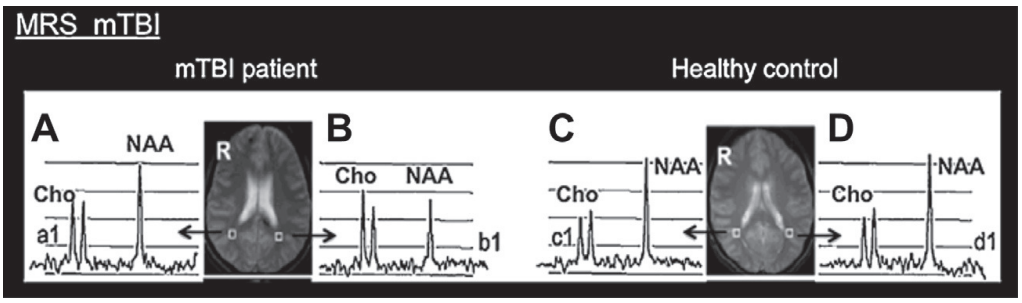

Fig. 4. Comparison of proton magnetic resonance spectra from a young patient with mTBI (*A, B*) and a healthy control subject (*C, D*) showing significant alteration of NAA and Cho in b1 compared with spectra a1, c1, and d1. The b1 voxel is located near injury seen on patient's T2 MRI in the left splenium. (*Adapted from* Govind V, Gold S, Kaliannan K, et al. Whole-brain proton MR spectroscopic imaging of mild-to-moderate traumatic brain injury and correlation with neuropsychological deficits. J Neurotrauma 2010;27(3):483–96; and *Reprinted from* Toledo E, Lebel A, Becerra L, et al. The young brain and concussion: imaging as a biomarker for diagnosis and prognosis. Neurosci Biobehav Rev 2012;36(6):1510–31; with permission.)

widespread research and clinical use because it does not require exposure to any radioactive substance, as do other functional techniques, and because it has a temporal resolution limited only by brain hemodynamics and a spatial resolution comparable to that of conventional MRI.[90]

Evidence is mounting that fMRI is sensitive to changes in neural function following TBI and holds promise as a tool for understanding mTBI and investigating recovery of function. fMRI studies are providing insight into the neural basis of cognitive and behavioral dysfunction following TBI (eg, **Fig. 5**). Although fMRI studies of mTBI are

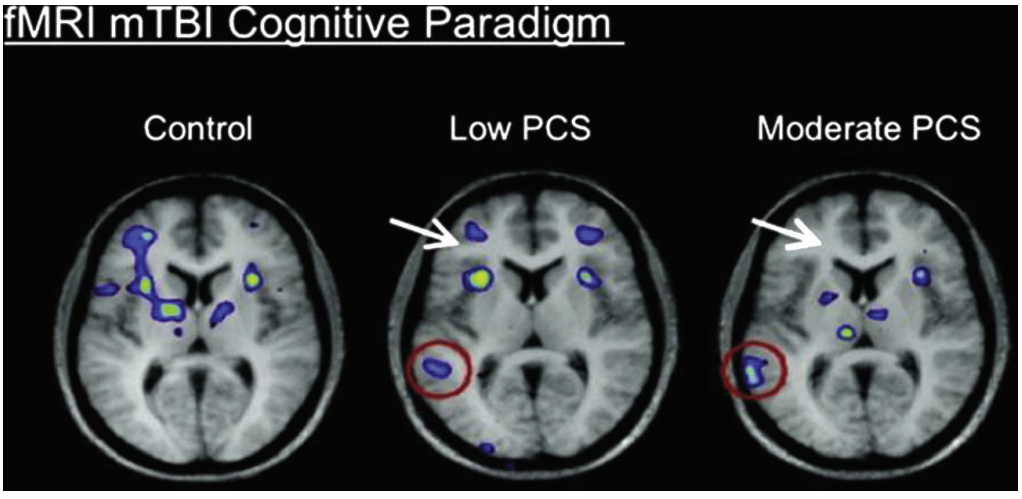

Fig. 5. Functional MRI comparing activation patterns during a verbal working memory task in healthy controls, patients with mTBI and low postconcussive symptoms (PCS), and those with moderate PCS. Additional activation in the posterior brain regions (*red circles*) and less activation in the frontal regions (*white arrows*) is seen in patients with low and moderate PCS compared with control subjects. (*From* Chen JK, Johnston KM, Collie A, et al. A validation of the post concussion symptom scale in the assessment of complex concussion using cognitive testing and functional MRI. J Neurol Neurosurg Psychiatry 2007;78(11):1231–8; with permission.)

scant, the studies that have been done have shown weaker BOLD changes in the dorsolateral prefrontal cortex, a crucial area for monitoring information in working memory.[91]

Studies in concussed athletes showed that they had significantly higher activation in the parietal cortex, right dorsolateral prefrontal cortex, and right hippocampus during performance of visual and spatial memory tasks compared with healthy controls.[92] The response to higher processing tasks in TBI suggested that these subjects did not have actual deficits in working memory ability but that they lost ability to recruit additional neural resources during these tasks.[93] The severity of postconcussive symptoms in concussed subjects was correlated with activation of the posterior parietal cortex. Additionally, activation of an area of the medial premotor cortex (Brodmann area 6) is correlated with longer recovery times, as measured by return to play. The latter findings are from a study that compared 28 concussed high school athletes with 13 age-matched controls while they completed the N-back task, a commonly used test of working memory. An additional important finding related to mood status or affect was noted. The presence of depressive symptoms in concussed athletes was singly related to fMRI activation on working memory tasks. Concussed nondepressed athletes performed comparably with healthy control subjects. These findings are contrary to those found in the acute postconcussive phase and suggest that in relatively young athletes, 2 to 6 concussions may not lead to a lifetime of cognitive deficits. This observation illustrates the plasticity of cognitive abilities in younger adults following concussion.[94]

A newer form of fMRI, called resting-state fMRI (RS-fMRI), is based on the analysis of spontaneous low-frequency fluctuations in the BOLD signal in the absence of any external task (eg, **Fig. 6**). Thirty-five patients with acute mTBI and 35 healthy controls matched for age, gender, handedness, and education underwent RS-fMRI.[95] A decrease in functional connectivity was noted in the motor striatal network in the mTBI group. A cluster of increased functional connectivity in the right frontoparietal network was also noted in the mTBI group, an abnormal finding that might reflect increased awareness to external environment and explain excessive cognitive fatigue reported by patients with mTBI. This increased connectivity also may underlie the physical postconcussive symptoms of headache, photophobia, and sonophobia. Whole-brain functional connectivity is altered within 4 weeks after mTBI, suggesting that changes in functional networks underlie the cognitive deficits and postconcussive complaints reported by this patient population. A recent study showed abnormal thalamic resting-state networks that point to subtle thalamic injury in patients with symptomatic mTBI, suggesting thalamocortical connectivity abnormalities, which may help to explain the complex persistent postconcussive syndrome.[96]

Future fMRI studies should address psychosocial factors, including psychiatric symptoms, such as posttraumatic stress disorder, as well as other potential confounding variables, such as conversion disorder and factitious disorders related to head injury. Genetic variation is another highly probable source of individual differences in mTBI and recovery profiles, and pharmacogenomics combined with fMRI is likely to be incorporated into the development of personalized medicine approaches for mTBI. It is also important to examine (1) the interaction between mTBI and aging and (2) the acute, subacute, and chronic phases of TBI. Task-related activation, deactivation, and RS-fMRI should continue to be investigated for use in the study of changes in functional connectivity, as it may be an important biomarker in research on neurorehabilitative interventions, including behavioral and pharmacologic approaches. A final benefit is likely to arise from the multimodality imaging studies that combine structural, functional, and molecular techniques.[97]

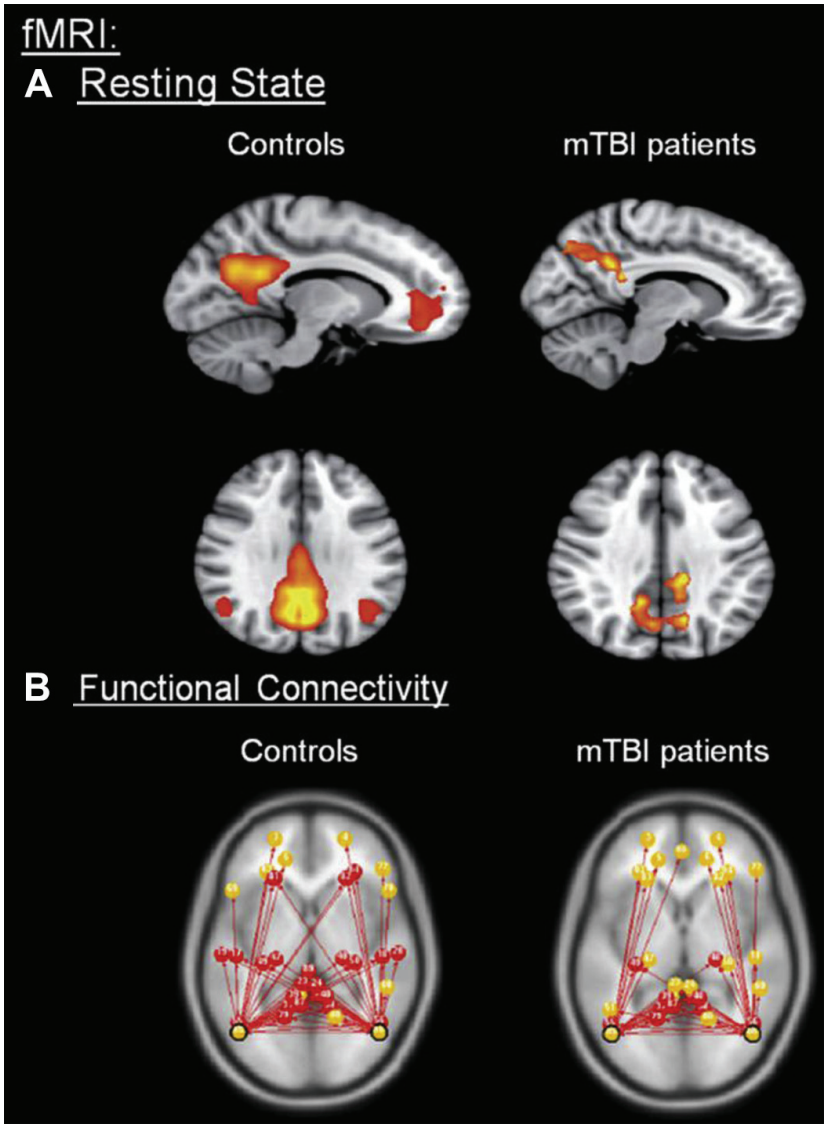

Fig. 6. (*A*) Resting state default mode network in control subjects with voxels showing significant functional connectivity in red–yellow. For patients with TBI, voxels showing greater connectivity than controls are shown in red–yellow. Note increased functional connectivity in posterior cingulate cortex and precuneus in patients, hypothesized to be a reflection of TBI and adaptive response to cognitive impairment. (*B*) Functional connectivity maps comparing resting state networks of healthy volunteers and patients with mTBI show differences between shared (*red*) and non-shared (*yellow*) connections from left and right parietal ROI. (*From* [*A*] Sharp DJ, Beckmann CF, Greenwood R, et al. Default mode network functional and structural connectivity after traumatic brain injury. Brain 2011;134:2233–47, with permission; and [*B*] Johnson B, Zhang K, Gay M, et al. Alteration of brain default network in subacute phase of injury in concussed individuals: resting-state fMRI study. Neuroimage 2012;59(1):511–8, with permission; and *Reprinted from* Toledo E, Lebel A, Becerra L, et al. The young brain and concussion: imaging as a biomarker for diagnosis and prognosis. NeurosciBiobehav Rev 2012;36(6):1510–31.)

Perfusion-Weighted Imaging

CT perfusion provides functional information about CBF and can help to identify patients with impaired autoregulation. Continuous scanning of a single slice or contiguous slices can yield time-density curves for each pixel within the image. Cerebral

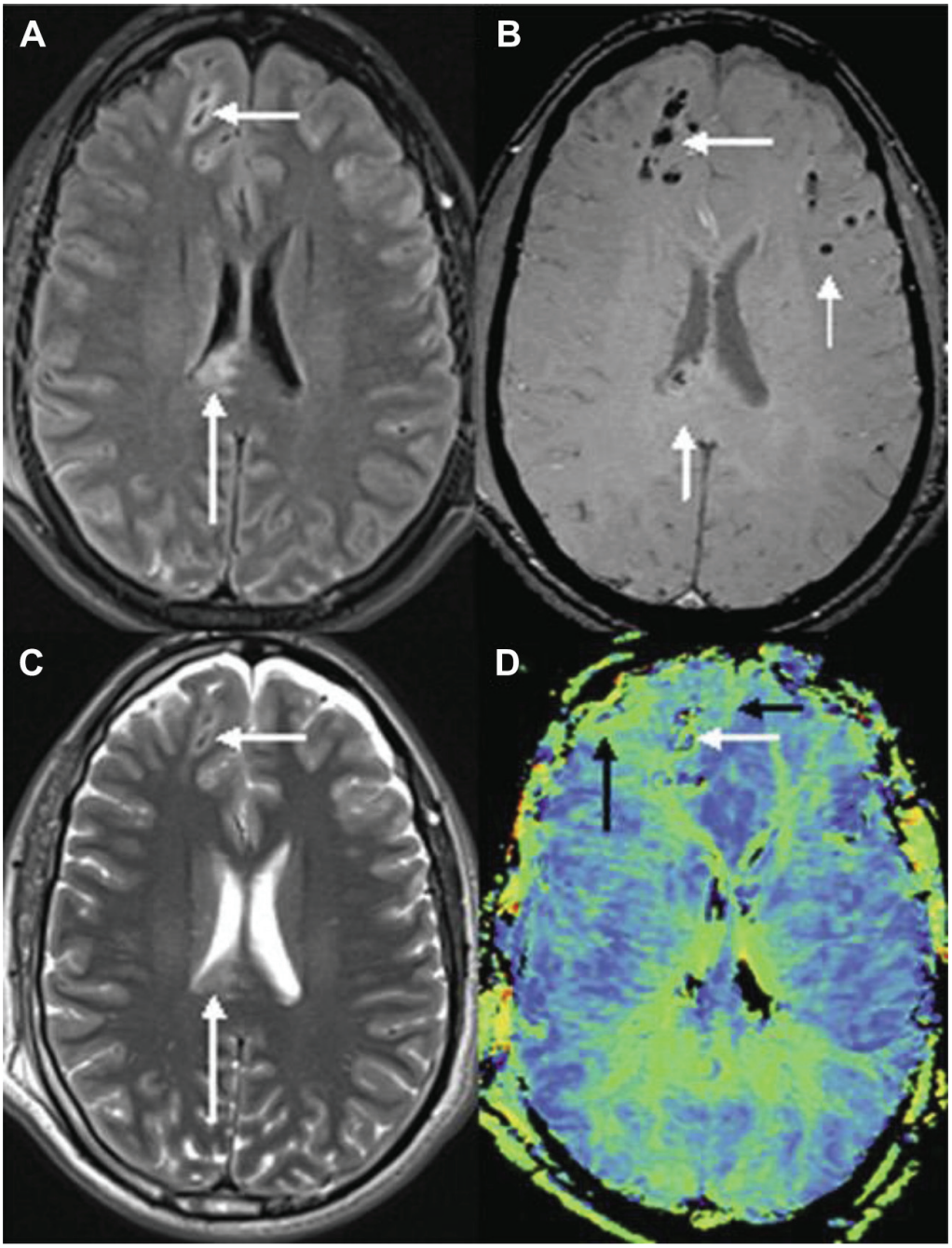

Fig. 7. Frontal medullary vein damage and microbleeds in a patient with TBI. (*A*) FLAIR image and (*C*) T2-weighted scan showing 2 of the damaged frontal areas (*short arrow*) and enhanced signal in the splenium of corpus callosum (*long arrow*). (*B*) SWI showing multiple bleeds in the frontal, lateral, and the splenium of the corpus callosum (*short arrows*). (*D*) Mean transit time images from the PWI data showing possible delayed arrival times in frontal regions and medial gray matter regions (*black arrows*) representing reduced perfusion to these tissues. Note the dark regions correspond to the bleeds (eg, area denoted by *white arrow*), and because of the long echo times used for PWI, the signal there was too small to be used to determine PWI parameters correctly and hence are set to zero here. (*From* Haacke EM, Raza W, Wu B, et al. The presence of venous damage and microbleeds in traumatic brain injury and the potential future role of angiographic and perfusion magnetic resonance imaging. In: Kriepke CW, Rafols JA, editors. Cerebral blood flow, metabolism, and head trauma: the pathotrajectory of traumatic brain injury. New York: Springer; 2013. p. 75–94; with permission.)

blood volume (CBV), CBF, mean transit time (MTT), and time to peak (TTP) are measured based on the passage of contrast bolus within the brain.[98] Studies have shown that normal brain perfusion or hyperemia is associated with favorable outcomes, whereas oligemia is associated with unfavorable outcomes. In the acute phase of mTBI, disturbed cerebral perfusion is seen in patients with normal noncontrast CT, correlating with the severity of injury and outcome. In patients with decreased GCS scores, a significant decrease of CBF and CBV can be detected in the frontal and occipital gray matter.[99] Xenon-131–enhanced CT assesses the distribution of inhaled Xe^{131} in the bloodstream and tissues and is often cited as the standard for quantitative measurement of CBF. Xenon-131–enhanced CT demonstrates regional hypoperfusion, typically more pronounced in pericontusional tissue.[100]

MR perfusion-weighted imaging (PWI) using arterial spin labeling is a technique that uses an endogenous contrast mechanism in which blood cells flowing into the brain are labeled by the MR signal without need for administration of an external contrast agent, making this method completely noninvasive and repeatable. Regional flow distributions can be assessed independently (eg, **Fig. 7**). In addition, truly quantitative values of CBF can be obtained.[101] Only a few studies have been published, but it has been demonstrated that hemodynamic impairment can occur and persist in patients with mTBI, the extent of which is more severe in the thalamic regions and correlates with neurocognitive dysfunction during the extended course of the disease.[102] In addition, regional hyperperfusion has been reported in the posterior cingulate cortices, thalami, and multiple locations in the frontal cortices.[103] PWI within 1 to 3 hours after injury shows far more severe and widespread perfusion deficits compared with imaging studies that are undertaken 24 hours after head injury.[104]

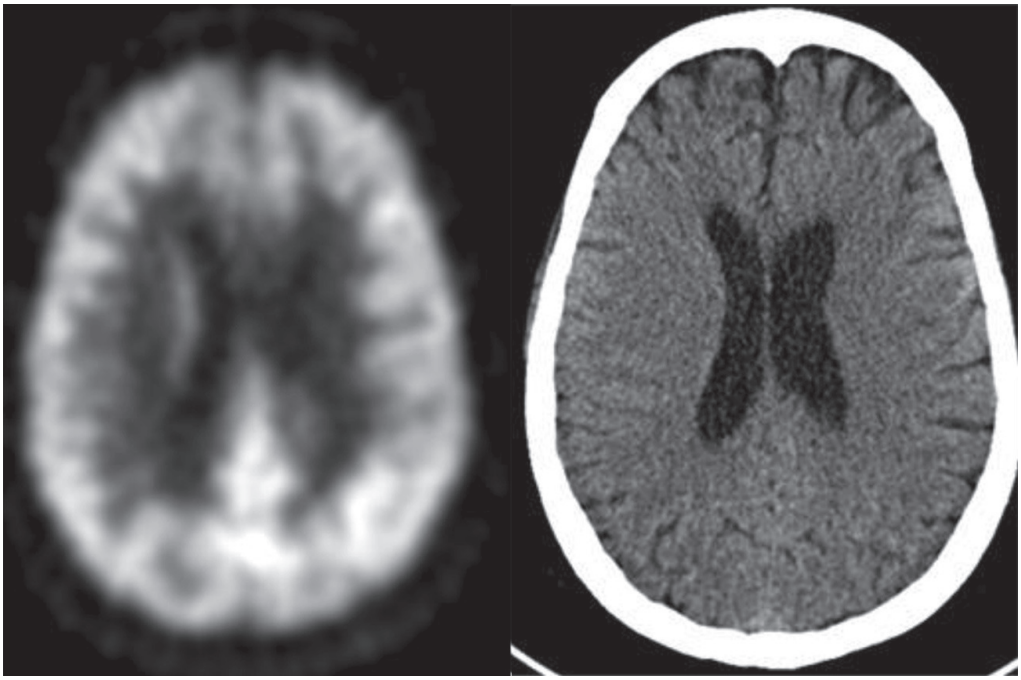

Fig. 8. A 43-year-old woman involved in a motor vehicle accident 2 years earlier presenting with headaches, diplopia, poor balance, and memory impairment. CT (*right*) reveals subtle loss of frontal volume. PET (*left*) reveals mild, patchy frontal cortical hypometabolism with moderate decrements in right polar and medial frontal cortex. Patchy, irregular white matter hypometabolism is also seen.

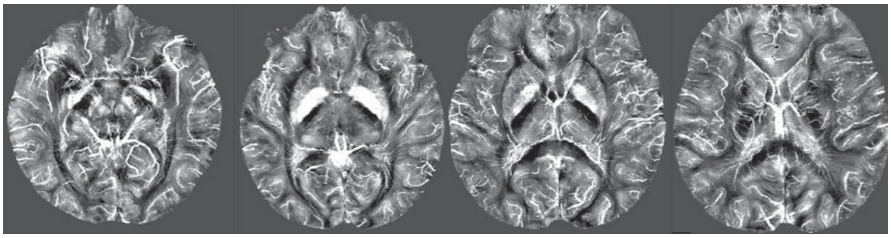

Fig. 9. QSM. Four slices from a 3D GRE multi-echo dataset acquired in a healthy volunteer at 7 T. The QSM maps created are shown as magnitude of tissue magnetic susceptibly with intensity. Vascular blood is thresholded from the QSM values and overlaid onto original QSM maps. (*Courtesy of* Liu C, PhD, and Moseley ME, PhD, Stanford, CA.)

Positron-Emission Tomography

Positron-emission tomography (PET) is a minimally invasive method that requires injection of a radioactive compound, with passive scanning performed at a predetermined interval following the injection. The most commonly used compound is [18F]-2-fluoro-2-deoxy-D-glucose (FDG). This compound provides data on regional brain utilization of glucose, a surrogate for brain metabolism. In sports-related concussion, early dysfunction may be secondary to altered cerebral utilization of glucose as a principal source of metabolic substrate for the production of ATP. The clinical conditions for which PET scans have performed well are those with altered cerebral metabolism. Cost, availability, and restricted use of radioactive materials have prevented more widespread use of this modality. No specific studies have reported the use of PET scanners in investigation or acute management of sports-related concussions. In TBI, clear abnormalities on O^{15} PET combined with FDG demonstrate regional and global alterations of metabolic activity. Diffuse cerebral hypometabolism carries a poorer prognosis for functional outcomes (eg, **Fig. 8**). In mTBI, a few small, chronic-stage disease studies have shown inconsistent findings, but they have shown correlation with cognitive tests.[105]

A recently developed compound, [18F]-fluoroethyl-methyl-amino-2-naphthyl-ethylidene-malononitrile (FDDNP), can highlight pathologic deposits of beta-amyloid and tau protein, and it shows promise as a marker for CTE. A recent small study revealed that FDDNP signals were higher in symptomatic retired National Football League players than they were in controls, in all subcortical regions and the amygdala, areas that commonly produce tau deposits in patients who have suffered TBI. The investigators rightly concluded that the study was limited by the small sample size and lack of autopsy confirmation.[106] Another newer compound, [18F]-THK523, shows promise as being specific for tau alone.[107]

EMERGING TECHNIQUES

The preceding discussion regarding observations made from DTI-based studies of mTBI substantiates that the ability to image the structural integrity of white matter tracts is a key development in the advanced neuroimaging of mTBI. DTI may no longer be the only structural imaging technique for assessing white matter tracts noninvasively in vivo. Similar to diffusion anisotropy, the magnetic susceptibility of white matter has been shown to be orientation dependent or anisotropic.[108] Variations in tissue magnetic susceptibility can be measured voxel-by-voxel to generate susceptibility tensors. Information obtained from susceptibility tensor imaging (STI) appears to be complementary to that obtained from DTI (**Fig. 9**). Thus, probing white matter

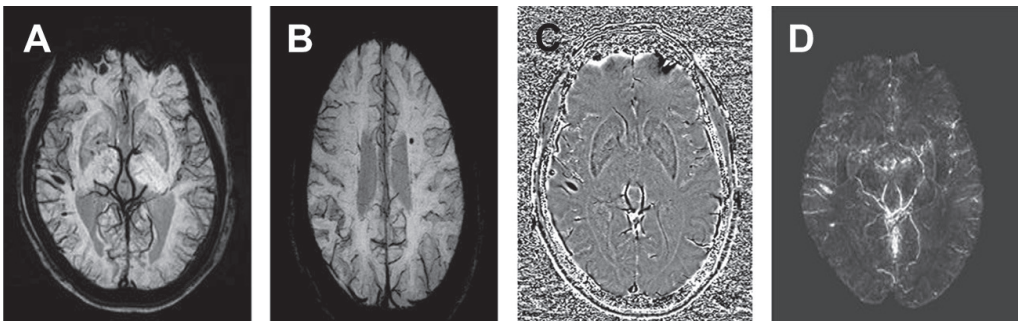

Fig. 10. A patient with motor vehicle accident–related TBI and postconcussive symptoms. (*A, B*) SWI showing microbleeds (hemorrhagic DAI). (*C*) SWI filtered phase and (*D*) SWIM. (*Courtesy of* Haacke EM, PhD, Detroit, MI.)

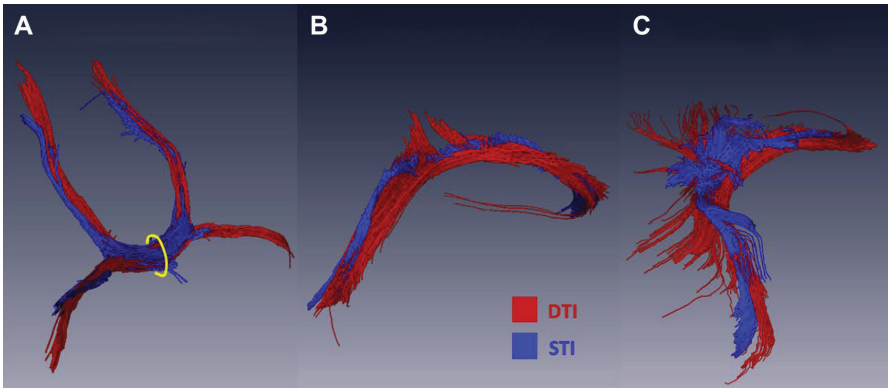

Fig. 11. Comparison of fiber tracts reconstructed using STI and DTI in (*A*) the anterior commissure, (*B*) the hippocampal commissure, and (*C*) the posterior corpus callosum. Yellow circle in (*A*) represents the middle of the anterior commissure. In general, the 2 methods of fiber tracking yield comparable results for large fiber bundles with STI fibers being generally shorter. In particular, for smaller and more complicated fiber structures, DTI results in longer and smoother pathways than does STI. (*From* Liu C, Li W, Wu B, et al. 3D fiber tractography with susceptibility tensor imaging. Neuroimage 2012;59:1290–8; with permission.)

microstructure simultaneously with susceptibility and diffusion imaging may provide a more complete characterization. Moreover, susceptibility imaging may have certain advantages over diffusion imaging. Resolution of DWI is fairly limited. Susceptibility images, on the other hand, can be readily acquired at much higher spatial resolution and are inherently 3D. As we move from high-field strength (3 T) to ultrahigh field strength ($\geq$7 T) magnets, susceptibility contrast will prove to be advantageous because of increased phase contrast and minimal sensitivity to field inhomogeneity.[108] Quantitative susceptibility mapping (QSM), alternatively referred to as susceptibility-weighted imaging and mapping (SWIM) (**Figs. 10** and **11**), is a novel technique that is showing promise in reducing the inconsistency of standard MRI sequences in cerebral microbleed burden measurements, and may find applications in the advanced neuroimaging of TBI.[109,110]

SUMMARY

TBI has attracted a great deal of social and mainstream media attention in recent years, partly because of our growing experience with war veterans with TBI and concerns regarding professional athletes' short-term risks and long-term morbidity as a result of concussions. The most common form of TBI in both military and civilian populations is mTBI. Most patients with mTBI become asymptomatic within a few days to weeks after injury, but an unfortunate 15% develop persistent disabling symptoms: the so-called "miserable minority."[111] Predicting which patients will develop persistent symptoms and which will recover fully has been a challenge. Even when long-term outcomes are known, conventional neuroimaging fails to distinguish patients with mTBI and persistent symptoms from those who recover, as the images are unremarkable in both cases. Further, in the absence of "organic" causes, many of the persistent symptoms have been branded as "psychogenic," complicating the management of these patients.

As in other subspecialties of neurology, advances in neuroimaging have provided new and improved structural imaging techniques that are being increasingly used in clinical practice for mTBI. At the same time, functional neuroimaging techniques are shedding new light on neurometabolic alterations and disturbances of functional connectivity in the brains of patients with TBI. The specific applications of various structural and functional imaging techniques in the evaluation of TBI are listed in **Table 2**. Some of the advanced structural and functional imaging techniques are not available for "prime time" clinical use, but it would not be overly optimistic to say that they will be applied for diagnostic and prognostic purposes in TBI within a few years.

As advanced neuroimaging unravels fine structural and functional abnormalities in a subset of patients with mTBI, and as efforts are under way to correlate these findings with clinical outcomes, the accuracy and adequacy of the term "mild traumatic brain injury" should be scrutinized. Although the classification of TBI patients as "mild" based on initial GCS score is undoubtedly useful in the acute setting, the terminology is rather inaccurate for those "mild" TBI patients who develop complicated and often very disabling symptoms. For similar reasons, the classification is inadequate in that it encompasses divergent clinical outcomes. The hope is that, in the near future, advanced neuroimaging will identify ways to further stratify the mTBI population into subgroups that are at low risk versus high risk for developing long-term sequelae. This specificity will allow clinicians to specifically target the high-risk patients for early treatment and improve outcomes. These advances are likely to emerge by way of development of biomarkers of injury, staging of reorganization, and reversal of white matter changes following injury, and tracking and characterizing changes in brain

Table 2
Applications of various neuroimaging techniques in evaluation of TBI

Technique/Modality	Principal Application in TBI
Structural	
CT	Intra/extra-axial hemorrhage, skull fracture, cerebral edema, herniation
MRI	
FLAIR	Contusion, nonhemorrhagic DAI, subarachnoid hemorrhage
DWI, ADC	DAI, cerebral edema
STIR	Orbital or calvarial trauma
GRE, SWI	Microhemorrhages (hemorrhagic DAI) from shearing
DTI	White matter integrity and connectivity
VBM	Atrophy, ventriculomegaly
Functional	
fMRI	Neuronal activation during functional tasks inferred from BOLD signal
CT/MR perfusion	Quantitative cerebral perfusion
MR spectroscopy	Neuronal loss, edema, inflammation, hypoxia
FDG-PET	Metabolic changes, task-related metabolism

Abbreviations: ADC, apparent diffusion coefficient; BOLD, blood oxygen level–dependent; CT, computed tomography; DAI, diffuse axonal injury; DTI, diffusion tensor imaging; DWI, diffusion-weighted imaging; FDG-PET, [18F]-2-fluoro-2-deoxy-D-glucose–positron emission tomography; FLAIR, fluid-attenuated inversion recovery; fMRI, functional magnetic resonance imaging; GRE, gradient-recalled echo; MRI, magnetic resonance imaging; STIR, short tau inversion recovery; SWI, susceptibility-weighted imaging; TBI, traumatic brain injury; VBM, voxel-based morphometry.

injury over time. Also, such tools will likely be used in future research to evaluate treatment efficacy.

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