Neuroimaging of brain trauma

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Purpose of review
The purpose of this review is to provide an update on advanced neuroimaging techniques in traumatic brain injury (TBI). We will focus this review on recent literature published within the last 18 months and the advanced neuroimaging techniques of perfusion imaging and diffusion tensor imaging (DTI).

Recent findings
In the setting of a moderate or severe acute closed head injury (Glasgow Coma Scale <13), the most appropriate neuroimaging study is a noncontrast computed tomography (CT) scan. In the setting of mild TBI, the indication for neuroimaging can be determined using the New Orleans Criteria or Canadian CT Head Rules or National Emergency X-Ray Utilization Study-II clinical criteria. Two advanced neuroimaging techniques that are currently being researched in TBI include perfusion imaging and DTI. Perfusion CT has a higher sensitivity for detecting cerebral contusions than noncontrast CT examinations. DTI is a sensitive at detecting TBI at the group level (TBI-group versus control group), but there is insufficient evidence to suggest that DTI plays a clinical role for diagnosing mild TBI at the individual patient level.

Summary
Future research in advanced neuroimaging techniques including perfusion imaging and DTI may improve the accuracy of the diagnosis and prognosis as well as improve the management of TBI.

Keywords
concussion, perfusion, traumatic brain injury

INTRODUCTION

Traumatic brain injury (TBI) is a major healthcare problem worldwide. In the United States, it affects 1.7 million people, hospitalizes 275 000 people and results in 52 000 deaths annually, and the incidence of emergency room visits related to TBI is on the rise [1–3]. Nearly 3 million people are living with long-term disability from TBI [4]. The top causes of TBI include motor vehicle accidents, falls, sports-related injury and assault in the civilian population and explosion-related injury in the military population [1–3,5]. Neuroimaging plays a critical role in the diagnosis, prognosis and management of TBI.

In the setting of a moderate or severe acute closed head injury (Glasgow Coma Scale <13), the most appropriate neuroimaging study is a noncontrast computed tomography (CT) scan in accordance with the American College of Radiology Appropriateness Criteria [6▪▪]. This scan can reveal life-threatening injuries such as expanding epidural hematomas and direct emergent neurosurgical evacuation. However, noncontrast CT scans have limitations [7▪]. For example, the size of parenchymal contusions can be underestimated with early CT scans [8]. For this reason, short interval follow-up CT scans may be beneficial. In addition, noncontrast CT is limited in detecting diffuse axonal injury [9]. Finally, early noncontrast CT imaging does not reliably show secondary ischemic changes related to cerebral edema and intracranial hypertension, which is responsible for nearly half of TBI-related deaths after admission [10].

In the setting of mild TBI, the indication for neuroimaging can be determined using the New Orleans Criteria [11] or Canadian CT Head Rules [12] or National Emergency X-Ray Utilization Study-II [13] clinical criteria. In the setting of a concussion, conventional CT and MRI are typically normal [14]. Although neuroimaging is not indicated for mild TBI in clinical settings, many researchers are exploring advanced neuroimaging techniques, especially

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KEY POINTS

- In the setting of a moderate or severe acute closed head injury (Glasgow Coma Scale <13), the most appropriate neuroimaging study is a noncontrast CT scan in accordance with the American College of Radiology Appropriateness Criteria.
- In the setting of mild TBI, the indication for neuroimaging can be determined using the New Orleans Criteria or Canadian CT Head Rules or National Emergency X-Ray Utilization Study-II clinical criteria.
- Perfusion CT has a higher sensitivity for detecting cerebral contusions than noncontrast CT examinations.
- DTI is a sensitive at detecting TBI at the group level (TBI-group versus control group), but there is insufficient evidence to suggest that DTI plays a clinical role for diagnosing TBI at the individual patient level.
- Future research in advanced neuroimaging techniques including perfusion imaging and DTI may improve the accuracy of the diagnosis and prognosis as well as improve the management of TBI.

since the majority of TBIs are mild in severity worldwide [15].

The purpose of this review is to provide an update on advanced neuroimaging techniques in TBI. We will focus this review on recent literature and on the advanced neuroimaging techniques of perfusion imaging and diffusion tensor imaging (DTI).

PERFUSION IMAGING

Clinical considerations

According to the American College of Surgeons, the primary goal for the treatment for patients with suspected TBI is to prevent secondary injury, which is largely preventable and treatable [16,17,18▪]. In fact, secondary ischemic changes related to cerebral edema and intracranial hypertension are responsible for nearly half of TBI-related deaths after admission [10].

In a healthy patient, cerebral blood flow is autoregulated by vasodilation and vasoconstriction such that cerebral blood flow (CBF) is maintained over a mean blood pressure ranging from 50 to 150 mmHg [16]. However, in the setting of TBI, cerebral autoregulation is compromised; thus, optimal management strategies include maintenance of normal CBF by avoiding systemic hypotension and low arterial oxygen saturation [16].

Another important clinical consideration is the relationship between the volume of an intracranial hematoma and intracranial pressure (ICP), known as the Monro–Kellie doctrine. Normally, the rigid skull is filled with the brain, cerebrospinal fluid (CSF) and intravascular blood. In the setting of an expanding intracranial hematoma, the ICP will initially remain normal as the expanding hematoma squeezes out CSF and intravascular venous blood. However, once this compensatory mechanism is exhausted, there is an exponential increase in ICP for even a small additional increase in the volume of a hematoma [16]. Cerebral perfusion pressure (CPP) is equal to the difference between the mean arterial pressure and the ICP. Thus, the exponential rise in ICP can lead to a significant drop in CPP and CBF and compromise oxygen and metabolite delivery [16].

A noncontrast CT scan cannot reliably assess early ischemic changes. The ability to image potentially salvageable tissue known as 'traumatic penumbra' and secondary ischemic events may one day help to improve clinical outcomes following TBI [19–21].

Imaging techniques of perfusion imaging

Perfusion imaging is a technique that is most commonly performed with CT or MRI. Perfusion CT (PCT) is performed via intravenous administration of a nondiffusible contrast (i.e. an agent that remains in the vasculature). In MRI, perfusion can be performed via intravenous administration of a nondiffusible gadolinium-based contrast agent via dynamic susceptibility weighted contrast [22]. Alternatively, magnetic resonance perfusion imaging can be performed without intravenous administration of contrast. In this noncontrast technique, known as arterial spin labeling, endogenous arterial blood water is magnetically labeled to serve as a diffusible flow tracer [22–27].

The central volume principle describes the link between a compartment volume, blood flow through the compartment and the mean transit time (MTT) through the compartment [28]. Key metrics in perfusion imaging include cerebral blood volume (CBV), regional CBF, MTT and time of maximum concentration (T_{max}) [29]. The CBV is calculated as the milliliters of blood per 100 g of brain tissue. The MTT is the average time for blood to flow from the arterial input to the venous drainage, which is equal to the CBV divided by the CBF [30–33]. The CBF is the milliliters of blood per 100 g of brain per minute. The T_{max} is calculated from the time to peak of the residue function, with $T_{max} = 0$ for normal perfused tissue without delay [34]. Perfusion imaging is most commonly performed in stroke evaluation [23,28,35,36], but also has applications in TBI [37▪].

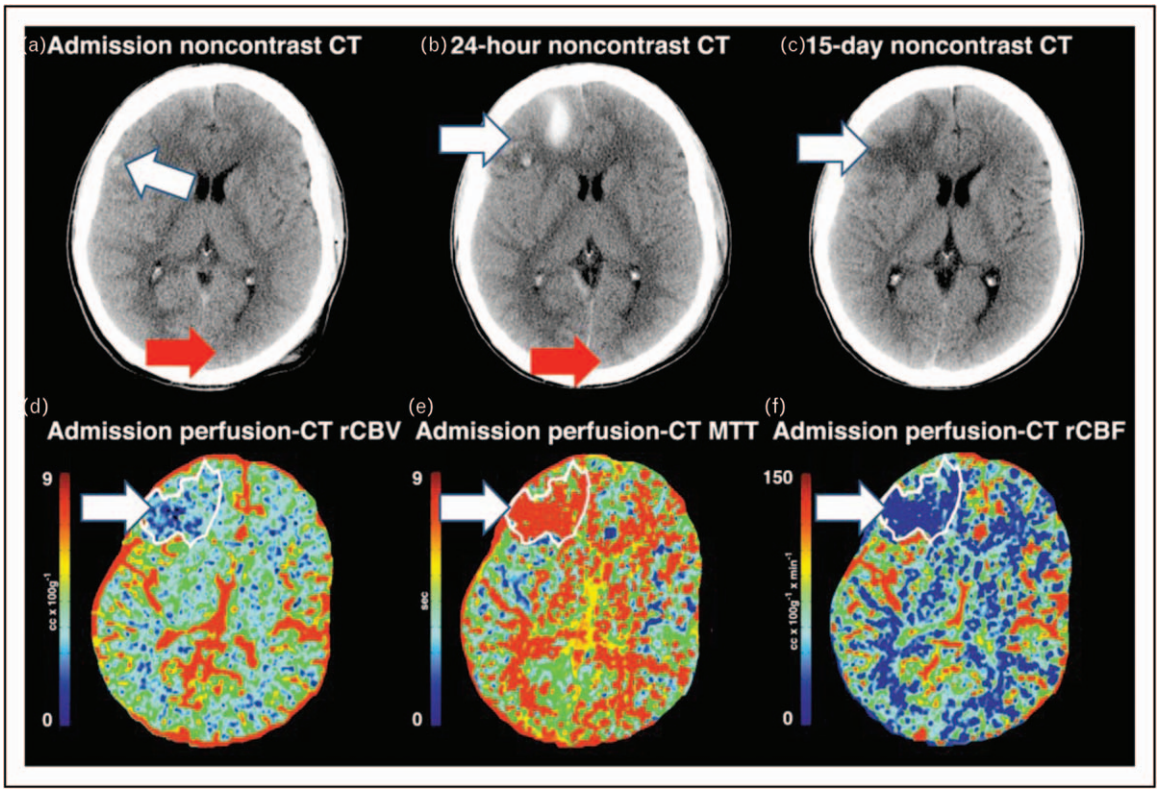

FIGURE 1. Contrast-enhanced and perfusion-computed tomography images from a patient with severe traumatic brain injury. (a) Noncontrast computed tomography at admission demonstrates a small hemorrhagic contusion in the right frontal lobe (arrow). Admission perfusion-computed tomography images demonstrate a large terrotory of decreased regional cerebral blood volume (d), increased mean transit time (e) and decreased regional cerebral blood flow (f). Follow-up noncontrast computed tomography at 24 hours (b) demonstrates increased areas of hemorrhagic contusion in the right frontal lobe in which the perfusion abnormality was seen. Follow-up noncontrast computed tomography at 15-days (c) demonstrates evolving hemorrhagic contusion and encephalomalacia in the right frontal lobe, which corresponds to the same distribution that is seen on the perfusion-computed tomography. Reprinted with permission [37▪].

Results of perfusion imaging of traumatic brain injury

A recent review by Douglas *et al.* [37▪] discussed potentials and challenges of perfusion imaging in TBI. Multiple studies have found scattered perfusion defects seen in TBI patients [17,38–43]. Perfusion abnormalities have been found to be associated with cerebral edema, juxtadural collections and intracranial hypertension [44,45▪] (Figs. 1–3). Areas of hypodensity on noncontrast CT may be necrotic or viable and PCT may help distinguish between these possibilities [46].

PCT also provides insight into the cerebral vascular autoregulation, which may be used to guide therapy and monitor treatment efficiency [46]. In moderate and severe TBI, this normal autoregulation is impaired and the brain is significantly more vulnerable to secondary brain injury.

Even in cases with no visible intracranial injury on admission noncontrast head CT, PCT with acute reductions in blood flow and blood volume were associated with worse outcomes [47,48▪]. Furthermore, in patients with severe TBI, PCT was found to show additional information in 60% of patients and alter management in 10% of patients [49,50▪].

Limitations of perfusion imaging in traumatic brain injury

With regard to PCT, the first limitation is the radiation dose. The aim of every institution should be to keep radiation dose As Low As Reasonably Achievable (ALARA); thus, adherence with recommended imaging protocols should be performed [51]. Another limitation of PCT is the intravenous administration of contrast material, which can result in renal impairment or allergic reaction [52].

With regard to perfusion MRI, the major challenge is the fact that MRI examinations are lengthy and pose safety issues in patients harboring ferromagnetic material or devices. Therefore, MRI examinations can be difficult to accomplish in the setting of TBI.

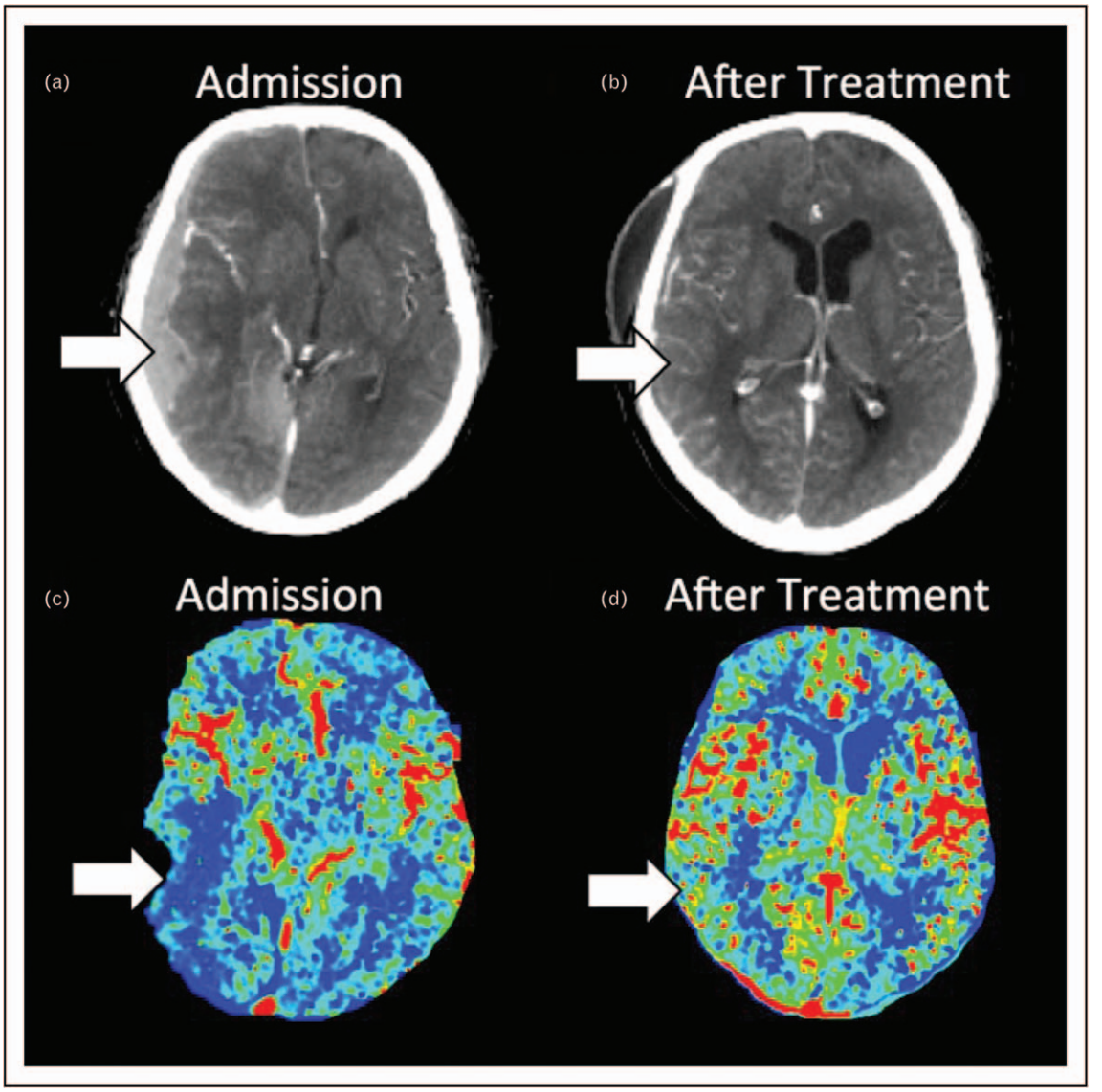

FIGURE 2. Contrast-enhanced and perfusion computed tomography images from a patient with severe traumatic brain injury. (a) Contrast-enhanced computed tomography imaging at admission demonstrates a right-sided subdural hematoma causing mass effect on the underlying brain and midline shift. (c) Regional cerebral blood flow perfusion computed tomography imaging at admission demonstrates decreased regional cerebral blood flow in the underlying right temporal lobe. (b) Contrast-enhanced computed tomography image after surgical evacuation of the hematoma demonstrates resolution of the right-sided subdural hematoma, mass effect and midline shift. (d) Regional cerebral blood volume perfusion computed tomography imaging after surgical evacuation of the right-sided hematoma demonstrates normalization of the regional cerebral blood flow in the right temporal lobe. Reprinted with permission [37▪].

DIFFUSION TENSOR IMAGING

Clinical considerations

The white matter of the human brain is composed of axons, which travel from gray matter in which the cell bodies of the neurons are located to other areas of the brain or spinal cord. White matter tracts consist of axon bundles traveling together, which putatively connect functionally specialized yet segregated regions of the brain. In the setting of TBI, such axons can be exposed to compression, tension, shear, bending and torsion forces; thus, there is strong rationale for performing DTI to assess axonal injury.

Imaging technique of diffusion tensor imaging

In conventional MRI, the contrast resolution is based solely on T1 and T2 relaxation times. As white

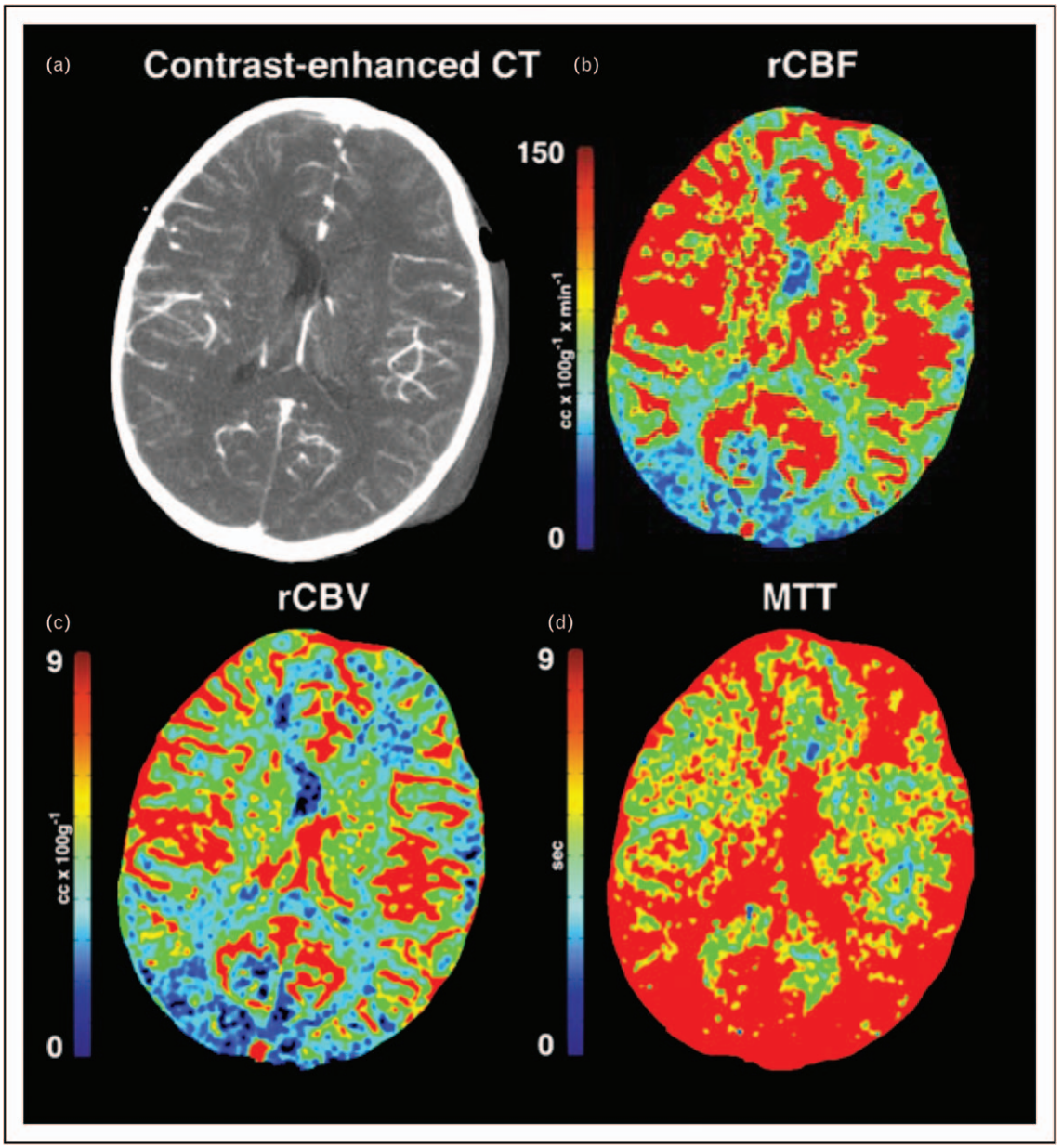

FIGURE 3. Contrast-enhanced and perfusion computed tomography images of a case of traumatic brain injury with intracranial hypertension. The contrast enhanced computed tomography (a) demonstrated left-sided scalp hematoma. The regional cerebral blood flow (b) and regional cerebral blood volume (c) trended toward lower values especially in the occipital lobes. The mean transit time (d) demonstrated significantly higher values, reflecting altered cerebral autoregulation after traumatic brain injury. Reprinted with permission [37▪].

matter tracts have similar T1 and T2 relaxation times irrespective of the direction of the tracts, the direction of the white matter tracts cannot be resolved.

DTI is a technique performed in MRI that quantifies the asymmetry and amount of water diffusion and provides rich information on the neuroanatomic connectome displayed in color-coded maps [53–62] (Fig. 4). The MRI technique is a spin-echo diffusion-weighted pulse sequence with diffusion weighting in multiple different spatial directions using diffusion-sensitizing gradients [63]. The DTI image has a typical thickness of 2.0 mm and a matrix of 128×128 [64,65]. For each diffusion-sensitizing gradient, there is a 4D data set with x, y, z spatial locations with a diffusion constant that is proportional to the magnitude or rate of water diffusion. This process is repeated with a minimum of six diffusion-sensitizing gradients and will ultimately yield a set of vectors that can be used to generate a structural connectivity map of the brain. However, modern DTI protocols have 30 directions to improve signal-to-noise ratio [66].

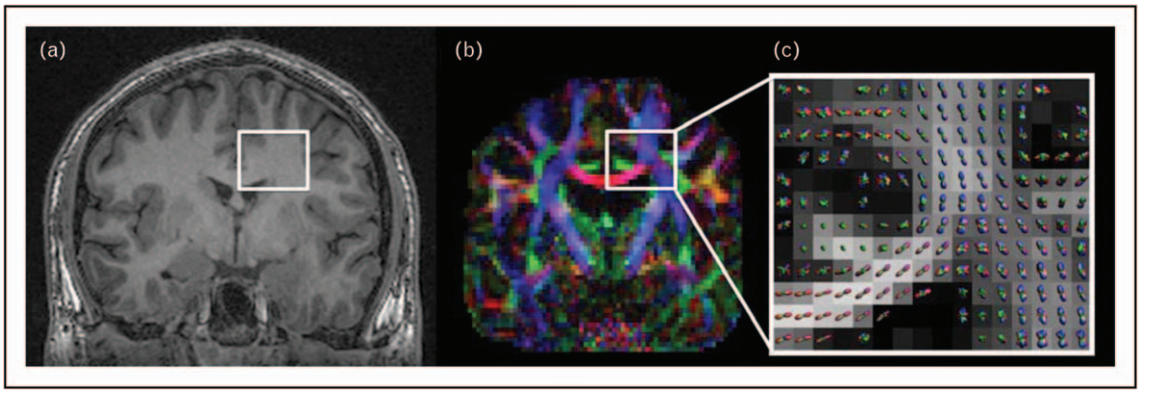

FIGURE 4. (a) T1-weighted coronal image through the corpus callosum. Note that the white matter contained within the white box is of similar intensity and the fiber tracts cannot be distinquished. (b) Q-ball type diffusion tensor image with conventional diffusion-encoded color map. Note that the direction of the fiber tracts are color coded. The red color corresponds to fiber tracts coursing transversely. The blue color corresponds to fiber tracts coursing superiorly–inferiorly. The green color corresponds to fiber tracts coursing anteriorly-posteriorly. (c) Zoomed in region from (b) with probability distributions in each voxel superimposed on a gray-scale fractional anisotropy map. The QBI acquisition parameters are as follows: 112×112 matrix; 22.4×22.4 cm field-of-view; 70 axial slices of 2-mm thickness; 6 b.0 images; 60 gradient directions at b.2500 s/mm^2; SENSE acceleration factor 2; TE/TR. 107 ms/10.3 s; and, acquisition time 11 m and 20 s. QBI, Q-ball imaging; SENSE, SENSitivity encoding; TE, echo time; TR, repetition time.

DTI metrics including factional anisotropy and mean diffusivity have been used to study a range of clinical conditions [67]. Fractional anisotropy is a measure of the asymmetry of diffusion [68]. Mean diffusivity is a measure of the amount of diffusion [68]. In healthy white matter, the diffusion is constrained by the organization of axons and factional anisotropy is high and mean diffusivity is low. In the setting of TBI, white matter factional anisotropy and mean diffusivity can be altered indicating axonal injury.

Many current DTI techniques are limited in the ability to assess fiber tracts crossing within a voxel [63,69–72]. There is considerable research in the development of newer DTI techniques, including diffusion kurtosis imaging, Q-ball, neurite orientation dispersion and density imaging and diffusion spectrum imaging [73–84].

Results of diffusion tensor imaging of traumatic brain injury

There have been numerous studies involving DTI in the TBI population with the shared finding of lower factional anisotropy and higher mean diffusivity in the TBI population as compared with the control group [85–102]. For example, a study of retired National Football League players revealed statistically significant reduced factional anisotropy in the bilateral frontal, bilateral parietal, corpus callosum and left temporal lobe in those players who were cognitively impaired group compared with controls [102]. Although many studies demonstrate decreased factional anisotropy and increased mean diffusivity in the TBI population as compared with the control group; the specific locations of decreased factional anisotropy are variable [85–102], which may be due to the heterogeneous nature of TBI.

Recently, a comprehensive literature review and meta-analysis of 44 studies of DTI changes in mild, moderate and severe TBI in a large variety of brain regions was performed [103▪▪]. In the mild TBI subgroup analysis, 88% of the brain regions examined had lower factional anisotropy values in the TBI group as compared with the control group. The moderate–severe TBI subgroup analysis showed 92% of the regions having lower factional anisotropy values than the control group. For the mean diffusivity, 95 and 100% of the regions examined were higher in the TBI group than the control group for mild and moderate–severe TBI, respectively.

Limitations of diffusion tensor imaging in traumatic brain injury

Although DTI is sensitive for TBI at the group level only for population-based research, there remains insufficient evidence at this time to suggest that DTI can be used to diagnose mild TBI in individual patients [63,104,105,106▪]. Furthermore, the finding of decreased factional anisotropy lacks specificity. Factional anisotropy alterations can be seen in a variety of other neurological conditions, particularly those that affect the white matter [107].

CONCLUSION

The TBI imaging literature demonstrates an overall high between-study heterogeneity with variable clinical heterogeneity including patient population, comorbidities, timing of TBI, mechanism of injury, site of injury and methodological heterogeneity to include imaging protocol, length of follow-up and modes of assessment. Such heterogeneity in TBI poses a challenge at identifying an effective treatment at an individual level [108]. Some neuroprotective strategies have resulted in positive outcomes in animal research, yet have failed to translate into improved clinical outcomes in clinical TBI trials [109–112]. One of the possible explanations is the fact that there is more heterogeneity in clinical settings as compared with consistent TBI models in animal research [109,113,114].

Steps forward include continued research into advanced neuroimaging techniques to improve the armamentarium of information collected during neuroimaging, such as information gathered via the advanced neuroimaging techniques of perfusion imaging and DTI. Advanced neuroimaging techniques create new opportunities for detection of injuries that might otherwise go unnoticed with conventional imaging. Through such techniques, more specific diagnoses can be made and coupled with more specific treatments.

Finally, the creation of normal age-stratified imaging databases may prove beneficial. With a normative database, computer-aided diagnosis and machine learning could be performed yielding a more refined diagnosis through etiological, symptom-based or prognostic classifications of TBI [115–118]. At the Joint ASNR-ACR-HII-ASFNR TBI workshop on 23 May 2014 in Montreal, Canada, there was a discussion on the formation of a consensus of the ideal database, normal control participants, and standardizing clinical and research neuroimaging protocols [119]. Machine learning refers to the process of training a computer algorithm to 'learn' from past experience in which neuroimaging parameters (e.g. CBV values) are matched to particular outcomes (e.g. Glasgow Outcome Scale). An integrated approach that combines optimal structural imaging, advanced neuroimaging parameters and clinical parameters may direct future treatment directions.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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