Current Clinical Applications and Future Potential of Diffusion Tensor Imaging in Traumatic Brain Injury

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Abstract: In the setting of acute central nervous system (CNS) emergencies, computed tomography (CT) and conventional magnetic resonance imaging (MRI) play an important role in the identification of life-threatening intracranial injury. However, the full extent or even presence of brain damage frequently escapes detection by conventional CT and MRI. Advanced MRI techniques such as diffusion tensor imaging (DTI) are emerging as important adjuncts in the diagnosis of microstructural white matter injury in the acute and postacute brain-injured patient. Although DTI aids in detection of brain injury pathology, which has been repeatedly associated with typical adverse clinical outcomes, the evolution of acute changes and their long-term prognostic implications are less clear and the subject of much active research. A major aim of current research is to identify imaging-based biomarkers that can identify the subset of TBI patients who are at risk for adverse outcome and can therefore most benefit from ongoing care and rehabilitation as well as future therapeutic interventions.

The aim of this study is to introduce the current methods used to obtain DTI in the clinical setting, describe a set of common interpretation strategies with their associated advantages and pitfalls, as well as illustrate the clinical utility of DTI through a set of specific patient scenarios. We conclude with a discussion of future potential for the management of TBI.

Key Words: diffusion tensor imaging, fractional anisotropy, mild traumatic brain injury, traumatic axonal injury

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The role of computed tomography (CT) and conventional magnetic resonance imaging (MRI) in the identification of central nervous system (CNS) injuries that require acute neurosurgical management has long been established in clinical practice. However, in the setting of mild traumatic brain injury (mTBI), CT and conventional MRI typically show no abnormality.[1,2] Likewise, in the setting of traumatic brain injury wherein a focal macro anatomic abnormality is present, the extent of additional focal and more diffuse microstructural abnormalities is often incompletely demonstrated by conventional imaging. mTBI results from blunt force trauma to the head or nonimpact acceleration/deceleration, with resultant disturbance of consciousness. The clinical importance and scope of mTBI, also termed concussion, is made evident by the significant morbidity it entails; as many as 30% of those who experience acute mTBI suffer from long-term persistent symptoms such as headache, cognitive impairment, depression, anxiety, post-traumatic stress disorder, and visual disturbances.[3] Such clinical manifestations of mTBI are attributed to microscopic traumatic axonal injury (TAI),[4] which is not always detectable on conventional imaging, but causes brain network dysfunction. In addition, in the setting of acute CNS trauma when conventional imaging modalities demonstrate a focal macro anatomic abnormality, the presence of additional focal or diffuse microstructural abnormalities often remains undiagnosed at the time of injury and on follow-up.

Consequently, more sensitive imaging modalities are required to detect subtle but clinically important white matter alterations in TBI patients. Diffusion tensor imaging (DTI) demonstrates structural white matter abnormalities in TBI patients both when standard anatomic imaging is positive and when CT and conventional MRI examinations are unremarkable.[4,5] Individuals harboring unrecognized diffuse white matter injury (ie, TAI) are likely at an increased risk for long-term cognitive and functional impairment. It is therefore not surprising that focal brain injury that is readily detectable on conventional CT and MRI is a poor predictor of clinical outcome.[4] Identifying TBI patients with microstructural white matter injury should thus prove useful in not only identifying signs of TAI but also in stratifying those at risk for adverse long-term clinical sequelae.

DIFFUSION TENSOR IMAGING METHODS

Diffusion tensor imaging has emerged as a powerful technique to detect microstructural white matter injury in TBI patients. DTI probes the directional coherence of motion of water molecules to provide information regarding tissue microstructure. At least 6 diffusion-sensitizing gradients, preferably more than 25, are applied along unique directions to create the DTI dataset. These data are used to compute the diffusion tensor, a mathematical representation of the 3D directional spectrum of diffusion, for all water protons within each voxel. The tensor may be graphically represented as a 3D ellipsoid, defined by 3 eigenvectors, $\lambda 1$, $\lambda 2$, and $\lambda 3$. The principal eigenvector, $\lambda 1$, is central to DTI tractography. Fractional anisotropy (FA), a summary measure describing the shape of the diffusion ellipsoid, provides information regarding the directional coherence or uniformity of water diffusion across a voxel, which reflects underlying tissue microstructure[6] (Fig. 1).

FA, scaled from 0 to 1, describes the relative uniformity of water diffusion within a given voxel. $FA = 0$ describes a state of random Brownian motion of water molecules, whereas $FA = 1$ describes perfectly uniform diffusion along a single direction. Neither of these extremes is encountered in tissue. Structural features of white matter, including the axolemma, myelin, microtubules, and neurofilaments, provide a highly ordered microstructural environment, resulting in a high degree of directional coherence of water diffusion along the length of white matter fibers. Therefore, within normal white matter, relatively high FA is expected, though the magnitude of FA varies by brain region. Disruption or loss of white matter microstructure in the wake of TBI results in a decline in the directional coherence of water

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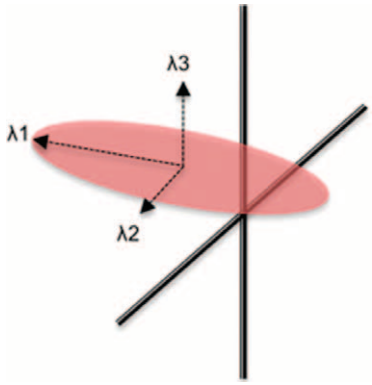

FIGURE 1. The diffusion tensor is graphically represented as a 3D ellipsoid, defined by 3 eigenvectors λ1, λ2, and λ3. Fractional anisotropy (FA) describes the uniformity of diffusion direction across the voxel, represented by the eccentricity of the ellipsoid.

diffusion and a consequent decrease in FA. These changes in FA are detectable after mTBI despite the absence of hemorrhage or frank tissue laceration as has been reported in an animal, for example,[7] and across multiple human studies, for example,[8] in which abnormally low FA correlates with important adverse outcomes after mTBI, such as cognitive impairment.

A large body of literature supports the use of DTI in detection of microstructural white matter injury in mTBI patients, as reviewed in refs.[4,9,10] The majority of prior reports documenting white matter abnormalities in mTBI patients[11–13] are largely based on group comparisons between controls and mTBI patients. However, evaluation of TBI in the clinical setting requires that DTI examinations be performed and assessed in individual patients. Several techniques have been described to evaluate TBI in individuals, using both qualitative and quantitative assessment.[14–17] In addition, numerous case reports have described the application of DTI to individual TBI patients.

ACQUISITION PARAMETERS

Several studies demonstrate at least some degree of reproducibility of DTI across imaging centers, MRI scanners, and across brain regions.[18–20] Of note, within-scanner reproducibility of FA and ADC has been shown to be higher than between-scanner reliability.[21] However, as with other advanced quantitative MRI methods such as DSC and MRS, standardization of absolute quantitative DTI parameter values remains a goal under study. Thus, in the clinical setting, data acquisition for an individual patient and the control group used for comparison is best performed at a single site on a single scanner. Careful attention must also be given to consistency of image acquisition parameters, processing techniques, and analysis for a given patient and the control group to which the patient is being compared.[22] Optimization of acquisition parameters, scanner maintenance, and rigorous ongoing quality assurance is necessary to ensure the integrity of the DTI images and results generated.

Magnetic Field Strength/Hardware

Although DTI can be performed on 1.5-T scanners, 3-T magnetic field strength is preferred. Stronger magnetic field improves signal to noise, increases achievable spatial resolution, and allows shorter acquisition time. Greater magnetic field inhomogeneity at higher field strength can be mitigated by use of a multi-channel head coil and parallel imaging. In addition, high-order shimming is advantageous to minimize magnetic field inhomogeneities, although not all vendors provide advanced shimming capabilities.

Gradient magnetic field hardware capable of high amplitude and speed is ideal for DTI, as these factors permit reduction of TE, thereby improving SNR and minimizing susceptibility artifacts; typically, 40 to 80 mT/m maximal amplitude and 150 to 200 mT/m/ms slew rate are the best achievable standards within FDA safety regulations.[23] However, stronger, faster gradients exacerbate issues related to eddy current generation due to electromagnetic induction. Eddy currents can lead to geometric distortions, including image shearing, scaling, and bulk shifting, the magnitude of which depends on the strength and direction of the diffusion-sensitizing magnetic fields.[24] These distortions may result in misregistration artifacts between the DTI images acquired along the various diffusion-weighted directions, which impact the calculated DTI parameter images. Thus, in addition to proper load compensation of the gradient system, distortion correction should be employed to correct eddy current effects before tensor fitting; magnetic field mapping is one of several strategies used for eddy-current related distortion estimation and correction.[25,26]

Echo Planar Imaging

DTI is most commonly performed using single-shot echo planar imaging (SS-EPI). Because diffusion imaging is highly sensitive to small bulk motion, a fast single-shot imaging technique such as EPI is required. Correction for patient motion related to issues such as CSF pulsation and respiration are nevertheless necessary. An additional advantage to EPI in DTI is that it maximizes SNR per unit scanning time in a technique that it is typically signal starved.

Number of Diffusion-Sensitizing Gradient Magnetic Field Directions and b-Value

Encoding the direction of diffusion requires a minimum of 6 diffusion-sensitizing directions, with greater SNR and enhanced directional resolution achieved with additional directions, at the cost of increased imaging time. Most commonly, 25 or more diffusion-sensitizing directions are used, with the acquisition of one additional $b = 0$ reference image for each 8 to 10 diffusion-encoding directions to mitigate the effects of a noisy $b = 0$ image.[27] Implementation of higher b values increases sensitivity to diffusion, but decreases SNR. Low SNR usually leads to overestimation of anisotropy, which can distort both the FA map and the eigenvalue estimations. Given these considerations, typical b-values range from 750 to 1000 m/s.

Spatial Resolution

Slice thickness of 2.0 mm is most frequently used, and voxel size typically ranges from 8 to 20 mm^3. Partial volume effects are more likely to occur with larger voxel sizes. The tensor computation for DTI assumes macroscopic homogeneity of fiber orientation within a voxel so that if a single voxel includes multiple fibers of varied orientations, spuriously low anisotropy within that voxel would be observed.[6]

DTI ANALYSIS

We describe 3 approaches to incorporate DTI into the evaluation of mTBI patients. Each approach is subject to limitations and pitfalls, which must be considered and accounted for in evaluating this population.

Qualitative Visual Inspection of the FA Map

Qualitative examination of the tensor parameter and color FA maps is 1 potential approach to clinical assessment of DTI (Fig. 2A). The most commonly used tensor parameters are mean diffusivity (direction-independent diffusion magnitude) and FA (directional coherence of diffusion). Color FA maps may be generated using post-processing software, with the conventional representation of diffusion direction based on hue (red: left-right; green:

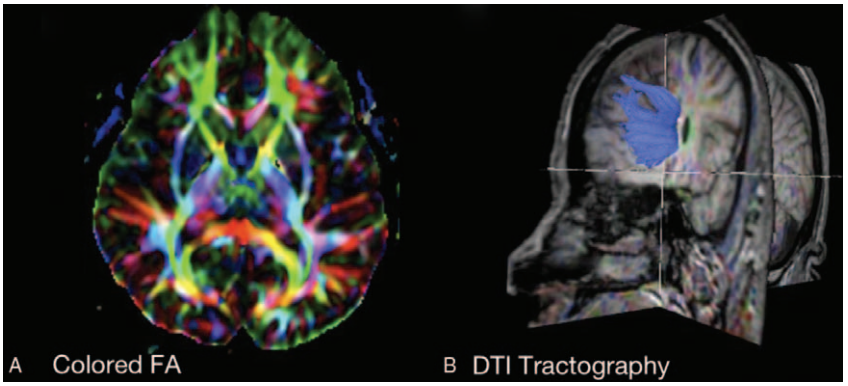

FIGURE 2. A, Color FA map: In addition to the magnitude of anisotropy, color FA maps reveal basic information about the predominant direction of diffusion (=direction of the principal eigenvector) at each voxel of the image. More detailed information may be provided by superimposing depictions of the diffusion vectors (not shown). B, Diffusion tractography reconstructs fiber tracts on the basis of the diffusion tensor.

anterior-posterior; blue: superior-inferior) and FA magnitude encoded as color intensity. Qualitative inspection of the FA map may reveal gross abnormalities. Unfortunately, FA images are noisy, and normal white matter appears quite heterogeneous on FA images. As a result, significant abnormalities are commonly difficult to detect by visual inspection alone. Moreover, visual identification of abnormally low FA is fraught with uncertainty and risk for false-positive and false-negative findings. Although visual inspection of the FA map may reveal abnormalities in more severe cases (see Fig. 3), it is not recommended as a standard primary clinical interpretation approach.

Diffusion Tractography

A second approach utilizes tractograms to assess bulk, completeness, and symmetry of specific white matter tracts using 3-dimensional renderings of these white matter tracts, based on the dominant direction of diffusion across contiguous voxels (Fig. 2B). In diffusion tractography, selected regions of interest (ROI) or seed points are used to trace diffusion trajectories on the basis of tensor shapes and orientations in each voxel; these algorithms can be specifically thresholded with termination criteria for minimum anisotropy (with the assumption that voxels below threshold represent CSF or gray matter) and maximum turning angle. Although there are several approaches to tractography, the most computationally straightforward and thus commonly employed strategy is the linear propagation approach, referred to as fiber assignment by continuous tracking (FACT), which is available in most clinical postprocessing software packages.[28] FACT can be applied in 1 of 2 ways: manual placement of an ROI-limiting voxel seeding or, in what is referred to as the ''brute force approach,'' seeding all voxels within the brain volume above a certain anisotropy threshold from which specific tracts can be subsequently selected.[29]

Tractograms may reveal truncation of specific white matter tracts and can dramatically display consequences of TAI including the result of Wallerian degeneration. However, it is important to recognize that tractography does not directly delineate axons or white matter fibers, but rather depicts features of water diffusion. Although these features generally reflect the orientation of underlying white matter anatomy, they are subject to the parameters employed in the tractography algorithm. There is significant potential for misleading artifacts secondary to parameter choice or to normal anatomical variation. Tissue heterogeneity within a voxel, such as crossing fibers or a subset of fibers with orientation different from the dominant fiber orientation, may lead to spurious results.[30] These issues can be at least partially addressed using other fiber reconstruction techniques commonly employed in the research setting, which are outside the scope of this paper.[28] Tractograms must be interpreted with caution and in the context of clinical information and a detailed knowledge of the technique, parameters employed, and normal anatomic variation. The most appropriate role of tractography may thus be to provide, in select cases, supplemental visualization of findings defined by quantitative analysis (below).

Quantitative Analysis

The third approach uses ROI or whole-brain voxelwise assessment of FA to determine variance of the patient's FA at a given location from the range of values across a normative sample.[14] Given strict adherence to technique, quantitative analysis provides a mathematical measure of FA abnormality and may serve as a more objective, nonqualitative diagnostic tool.

ROI analyses are advantageous in that a clinician can be more hypothesis-driven in terms of interrogation of specific brain regions thought to be related to symptomatology, and because it minimizes the statistical problem of multiple comparisons. However, quality assurance is necessary to ensure reliability of measurements. Potential sources of error-utilizing ROI analysis include choice of ROI, placement of the ROI, and partial sampling of voxels within the ROI.[30]

Whole-brain voxelwise analyses are technically demanding, but they eliminate the issue of operator bias. Voxelwise analyses require more specific attention to the issue of multiple comparisons, which increases the potential for type I errors. Thresholding for cluster size in addition to voxel-level significance helps to minimize false positives; optimization of such thresholds has been described.[31] Robust appropriate normative data must be available and should be acquired using identical methods and, potentially, scanner platforms for patients and controls, as described above. Testing of control datasets, such by using cross-validation, is a helpful approach to establishing and validating thresholds for abnormality. The development of standardized diffusion measures with use of phantoms is a subject of current research, but it remains to be demonstrated to what extent specific absolute DTI parameters are generalizable. Thus, at present, a robustly developed and validated normative cohort is the most reliable approach to identification of microstructural pathology that may lead to unexpected but clinically important findings.

CLINICAL APPLICATIONS

Once DTI is acquired and processed, as described above, a radiologist must interpret the information in the context of the clinical history available. Qualitative DTI information is displayed

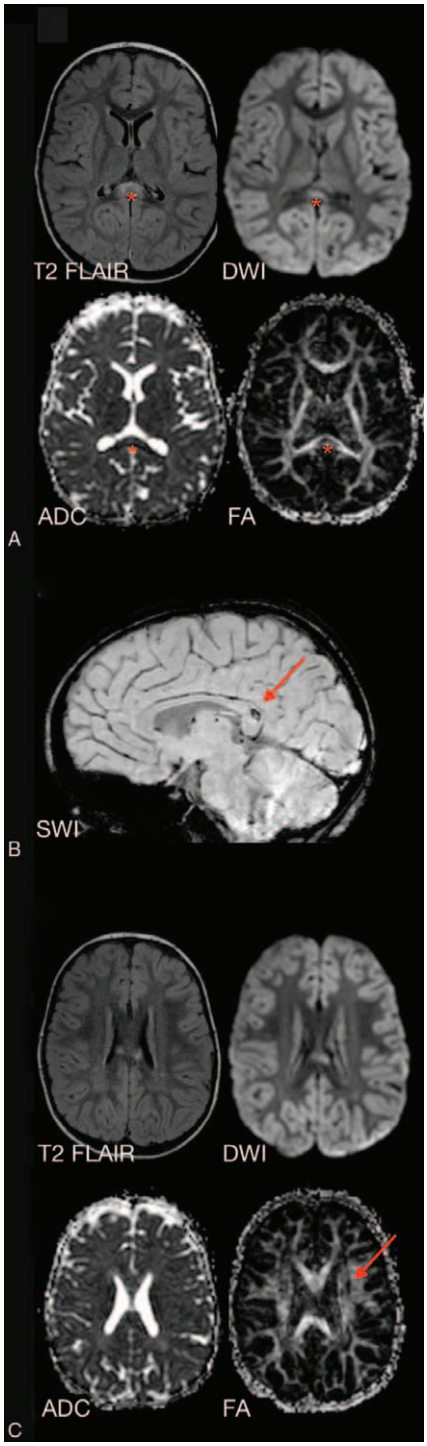

FIGURE 3. Nonaccidental injury, 2-year-old with multisystem injury due to abuse. Imaging was performed 3 days after injury. A, The FA map demonstrates low FA in the splenium consistent with microstructural white matter injury (TAI). However, the same lesion is clearly evident due to hemorrhage, restricted diffusion, and FLAIR hyperintensity (*). B, Hemorrhage is noted within the splenium of the corpus callosum (arrow). C, The FA map demonstrates low FA in the left corona radiata (arrow). Unlike A, no other imaging abnormalities are present at this location.

as a grayscale or a color map that can be overlaid upon a structural image of the brain. Because white matter structures have a greater directional coherence than grey matter, they are characterized by higher FA and appear as higher "intensity" on a grayscale FA map; lower FA appears as lower "intensity" or interruption of the expected color-encoded orientation on a color FA map. When lower FA occurs in a location that normally exhibits higher FA, it may be detectable as an abnormality. Although it is alluring to propose that FA abnormalities can be detected visually, similar to the identification of abnormalities on other MRI sequences, the inherent variability of FA in normal white matter makes visual perception difficult and unreliable; only in particularly severe cases will abnormalities be clearly visible.

As discussed above, DTI is sensitive to microstructural TAI not detected by conventional MRI. For instance, Figure 3 displays an FA map from a 2-year-old boy who was admitted with multisystem injury due to nonaccidental trauma. As expected, the white matter tracts are bright and areas corresponding to CSF and gray matter are dark. An area of hemorrhage is noted in the splenium of the corpus callosum, with associated restricted diffusion on DWI and hyperintensity on T2W-FLAIR. On the FA map, the splenium lesion is depicted as a dark focus, compatible with low FA (Fig. 3A). However, an additional area of low FA is identified in the left corona radiata, but, unlike the corpus callosum lesion, no colocated abnormalities are present in this location on other MRI sequences (Fig. 3C). Thus, qualitative visual inspection of the FA map detected an additional area of abnormality not detected via conventional MRI.

Visual inspection of parametric and color maps reveals at most only a small portion of abnormalities that may be present; within-subject heterogeneity of white matter FA renders focal decrease in FA difficult to perceive on visual inspection, necessitating quantitative approaches to reliably detect abnormalities. Figure 4 demonstrates the

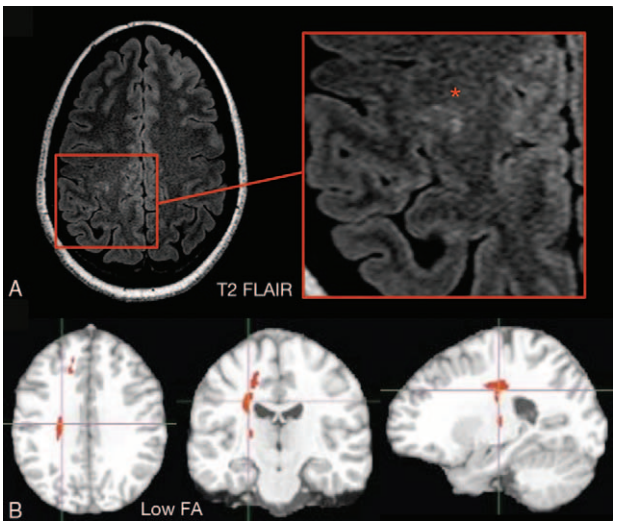

FIGURE 4. Added value of quantitative DTI, 30-year-old with trauma to the back of the head sustained during a MVA. Patient reported feeling dazed and confused immediately afterwards. DTI was performed 3 years after initial injury due to persistent postconcussive symptoms. A, Small areas of signal hyperintensity in the right centrum semiovale (*). MRI was otherwise structurally normal. B, Low FA colocates with hyperintensity seen on T2W-FLAIR. Inferior and superior extension of low FA may represent additional injury or Wallerian degeneration due to TAI. Low FA is seen in additional regions with no other imaging abnormalities (eg, right frontal lobe). Extensive low FA in the right centrum semiovale colocates with hyperintensity seen on T2W-FLAIR.

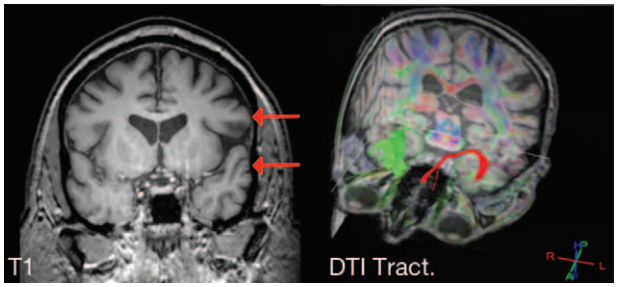

FIGURE 5. Impaired verbal memory after MVA—cautious use of tractography, 63-year-old retired helicopter pilot, rear ended in an MVA with subsequent severely impaired verbal memory. DTI was performed 3 years after initial injury. The left Sylvian fissure and adjacent frontal and temporal sulci are asymmetrically prominent, indicating volume loss (red arrows). DTI tractography of the uncinate fasciculus demonstrates asymmetry of the right and left tractograms, with the left smaller than the right. This finding is consistent with the regional atrophy and the verbal memory deficit in this patient. Asymmetry of the uncinate fasciculus is expected s a normal finding. However, in this right-handed man, the left uncinate fasciculus would be expected to be larger, not smaller, than the right, paralleling hemispheric language and memory dominance.

value of quantitative DTI in a 30-year-old woman who sustained trauma to the back of her head during a motor vehicle accident. Qualitatively, the FA map appears normal. Quantitative analysis of DTI demonstrates low FA in the right centrum semiovale, colocalizing with hyperintensity seen on T2W-FLAIR images. Additional areas of low FA are also demonstrated in the right frontal lobe without corresponding abnormalities seen on FLAIR imaging. Inferior and superior extension of low FA in this case may represent additional injury or Wallerian degeneration due to TAI. Quantitative measures are thus more sensitive than visual inspection, both in characterizing abnormalities seen on other sequences and in revealing abnormalities indiscernible on other sequences.

In addition to visual inspection of FA maps and their quantitative analysis, tractography may be used to visualize posttraumatic abnormalities,[5] as previously described. The clinical application of tractography is illustrated in Figure 5, which shows coronal T1W images and tractograms in a 63-year-old retired helicopter pilot who was injured in a MVA and subsequently presented with severely impaired verbal memory. T1W images demonstrate the left Sylvian fissure and adjacent frontal and temporal sulci to be asymmetrically prominent, indicating volume loss. Tractography of the uncinate fasciculus in this patient demonstrates the left to be smaller than the right. Although asymmetry of the uncinate fasciculus is an expected finding, in this right-handed man, the left uncinate fasciculus would be expected to be larger, not smaller, than the right, paralleling hemispheric language and memory dominance. In the appropriate clinical setting, tractography may demonstrate abnormalities of specific white matter tracts and explain specific structure-related symptoms.

Potential pitfalls in tractography relate to interuser variability in ROI placement and parameter choice in the tracing algorithm. Figure 6 exemplifies artifactual tract truncation in the case of a 44-year-old man who sustained a displaced orbital roof fracture after falling from a 15th floor scaffold. Head CT at the time of injury demonstrated right frontal intraparenchymal air and bifrontal hemorrhagic contusions. Axial T2-weighted fast spin echo images obtained 2 and a half years after the injury demonstrated right frontal encephalomalacia with surrounding hemosiderin deposition, compatible with orbitofrontal laceration. Tractography revealed apparent

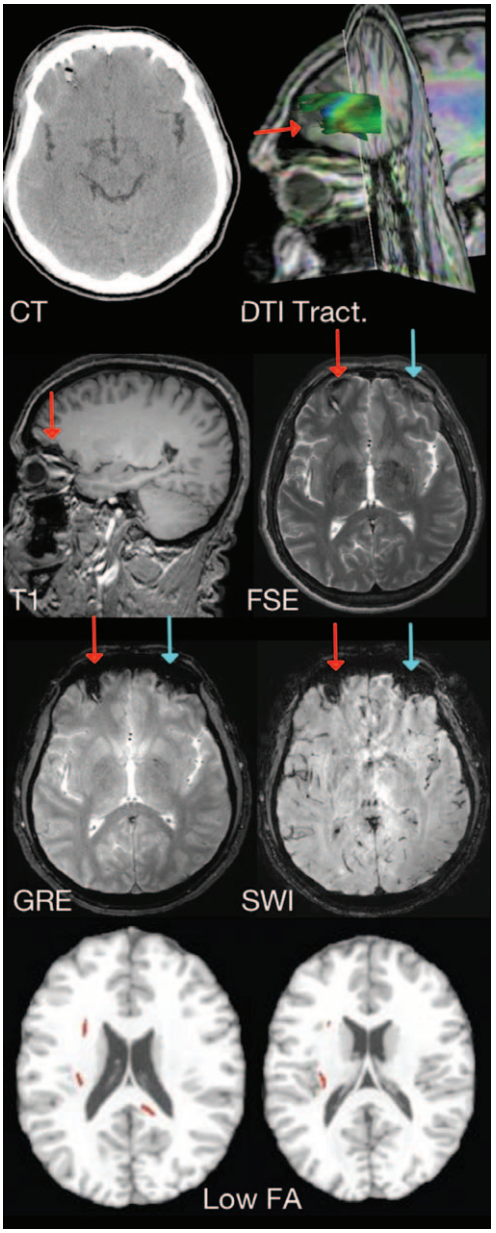

FIGURE 6. Limitations of tractography, 44-year-old fell 15 ft from a scaffold, resulting in a displaced right orbital roof fracture. DTI was performed 2.5 years after injury. Orbitofrontal laceration (red arrow): Head CT demonstrates right frontal intraparenchymal air indicating laceration of orbitofrontal cortex as well as bifrontal hemorrhagic contusions. Encephalomalacia with surrounding hemosiderin deposition is present in the right orbitofrontal cortex. Bifrontal hemorrhagic contusion (blue arrow): Additional areas of susceptibility-related signal loss are present at the inferior aspect of the frontal lobes bilaterally, typical for a hemorrhagic contusion. Abnormally low FA in the splenium of the corpus callosum is particularly characteristic of TAI. Similar abnormalities were also visualized in the right corona radiata, the right external capsule, and in the internal capsules bilaterally. Tractography demonstrates apparent truncation of the forceps minor on the left side, although quantitative analysis did not confirm abnormally low FA in this location. It is unclear whether the tractographic appearance represents a true abnormality or artifact due to premature termination of the tractography algorithm.

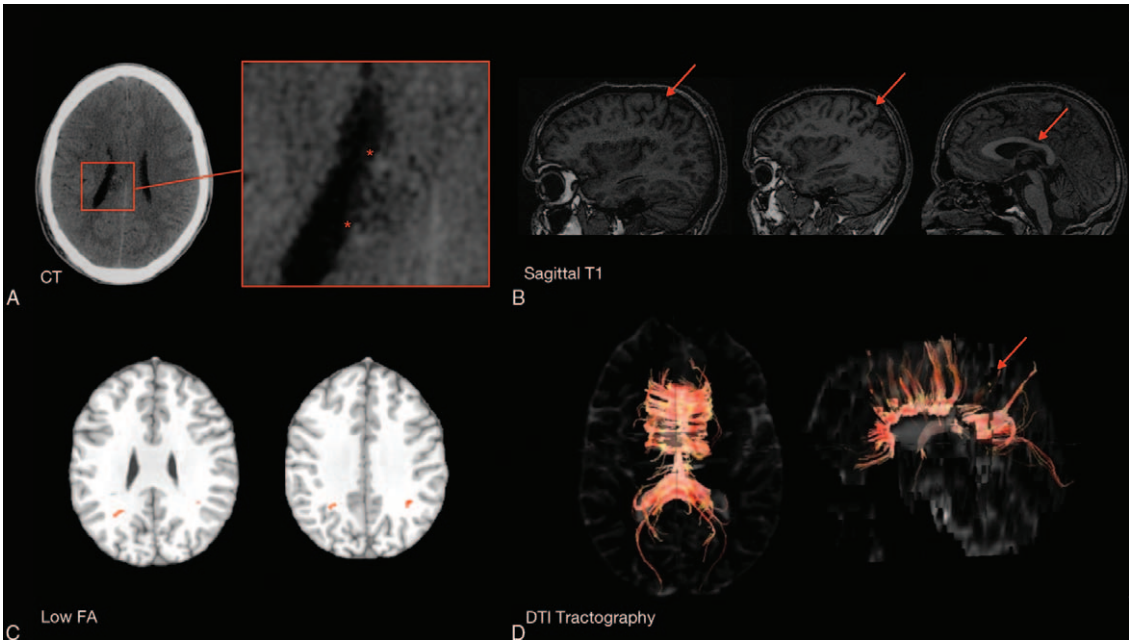

FIGURE 7. Combined use of tractography and quantitative DTI; 22-year-old male fell 25 feet from a scaffold, landing on the vertex of his head. A, Initial head CT on the day of injury demonstrates 2 petechial hemorrhages in the body of the corpus callosum. CT scan the following day demonstrates the petechial hemorrhages (*) with evolving edema. B, Follow-up imaging 7 years later, due to persistent deficits in processing speed and fine motor function, demonstrates thinning of the posterior portion of the body of the corpus callosum (->) with associated biparietal cortical atrophy (->), consistent with Wallerian degeneration due to TAI involving the corpus callosum. C, Truncation of tractograms emanating from the region of the corpus callosum hemorrhages (->), consistent with Wallerian degeneration due to TAI. Tractographic abnormalities are colocated with the regional biparietal atrophy. D, Quantitative analysis demonstrates biparietal abnormally low FA, consistent with Wallerian degeneration along fibers projecting to the location of biparietal atrophy due to the corpus callosum injury.

truncation of the forceps minor on the left side. However, quantitative analysis did not confirm abnormally low FA in this area. Thus, it is unclear whether the tractography appearance represents a true abnormality or artifact due to premature termination of the tractography algorithm.

Caution must be exercised in the use of tractography, which may be best applied for visualization of quantitatively confirmed abnormalities (see Methods). Figure 7 illustrates the case of a 22-year-old male who fell 25 feet from a scaffold, impacting his head at the vertex. Head CT on the day of injury demonstrates 2 petechial hemorrhages in the body of the corpus callosum on the right. MRI was performed 7 years later due to persistent acquired deficits in processing speed and fine motor function. Sagittal T1-weighted images demonstrate thinning of the body of the corpus callosum posteriorly, with associated biparietal cortical atrophy. The attenuation of tractograms of the corpus callosum is consistent with Wallerian degeneration due to TAI. Quantitative analysis of DTI demonstrates abnormally low FA in the deep parietal white matter bilaterally, corresponding to the incomplete tractograms.

When patients suffer persistent symptoms due to TBI, but conventional imaging examinations are unrevealing, underlying undetectable microscopic TAI is the inferred pathologic substrate, which may in part be revealed using DTI. Figure 8 shows a 28-year-old female driver who was hit broadside by a cement truck, impacting the left posterior portion of her head. CT performed on the day of the accident revealed no intracranial abnormality. Five years later, the patient still exhibited persistent cognitive impairment. MRI showed no hemorrhage or gross structural abnormality. However, quantitative assessment of DTI demonstrated areas of abnormally low FA clustered posterolaterally on the left, consistent with the mechanism

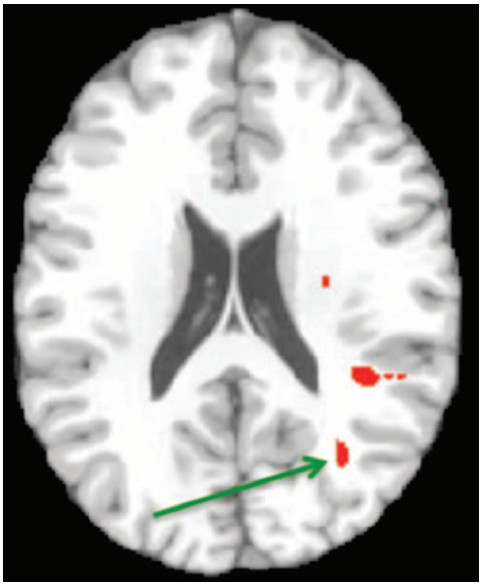

FIGURE 8. Considering quantitative DTI in clinical context, 29-year-old hit broadside by a cement truck, impacting the left posterior portion of her head. DTI was performed 5 years later, due to persistent cognitive impairment. DTI evidence of TAI: Structural images were unremarkable. Areas of abnormally low FA clustered on the left posteriorly. The location of abnormalities is consistent with the left posterolateral site of impact.

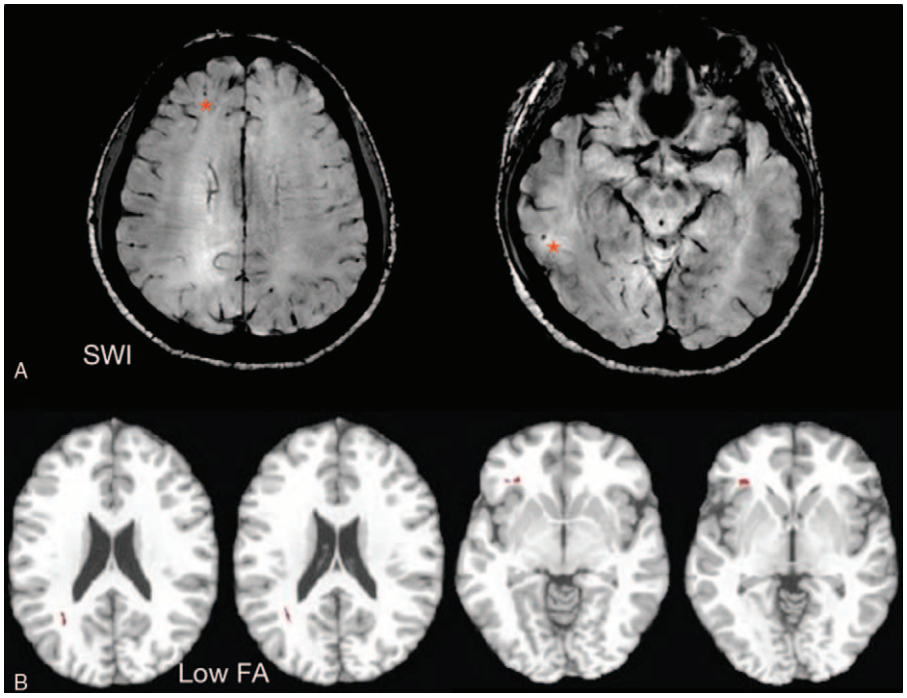

FIGURE 9. Quantitative DTI of normal appearing white matter, 24-year-old thrown from a jet ski at full speed hitting the right side of her forehead on a dock. Head CTs were reportedly negative x3 during her hospitalization. After 8 years, she has persistent deficits in language, learning, and memory. A, Multiple foci of hemorrhagic TAI (*) are demonstrated on SWI. FLAIR and FA images appeared normal. B, Frontal-parietal distribution of abnormally low FA on the same side as the head impact, consistent with the distribution of contusions in a coup-contrecoup injury.

of her injury and location of impact, demonstrating a pathologic basis for the patient's deficits. Similarly, Figure 9 shows a 24-year-old woman who was thrown from a jet ski at a high speed, impacting her forehead on the right. Despite multiple negative CT scans, deficits in language, learning, and memory persisted for 8 years. At that time, susceptibility-weighted images demonstrate several foci of petechial hemorrhage on the right, which were not evident on the acute CT. Although T2W-FLAIR and visual assessment of FA maps show no abnormality, quantitative analysis of DTI demonstrated frontal distribution of abnormally low FA ipsilateral to the side of head impact and hemorrhage, confirming the presence of hemorrhagic TAI and represent the expected distribution of contusion in coup-contrecoup injury. Thus, in the chronic setting, DTI has a role in detecting pathology that may have gone undetected or unrecognized in the acute phase, but caused significant persistent deficits nonetheless.

In addition to the subacute and chronic settings, DTI can be used to identify TAI in the acute postinjury time period, even in very mild traumatic brain injury, wherein recognition of brain injury might be helpful for patient triage. For instance, Figure 10 describes a 48-year-old toll booth collector who was hit in the right temple by a pipe jettisoned from a passing truck; although he experienced symptoms related to his head injury, including being dazed and

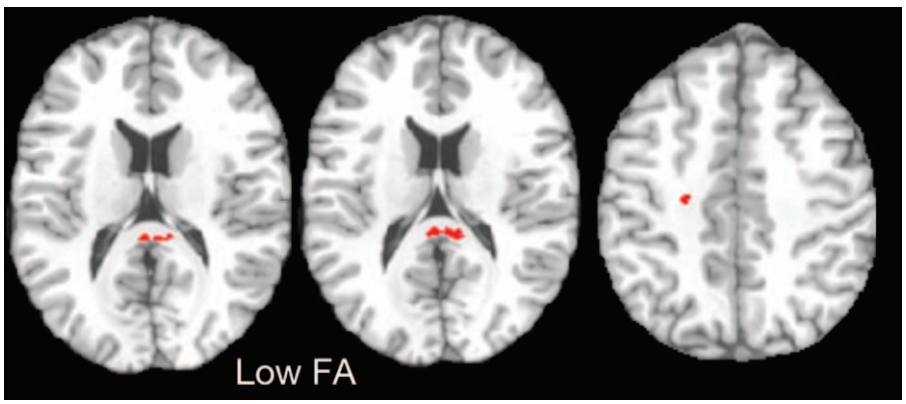

FIGURE 10. Quantitative DTI in the acute setting, 48-year-old toll booth collector hit in the right temple by a hydraulic pipe jettisoned from a passing auto carrier, without loss of consciousness. CT was normal. DTI was performed 8 days after injury. Abnormally low FA in the right centrum semiovale and the splenium of the corpus callosum, sites typically affected by TAI.

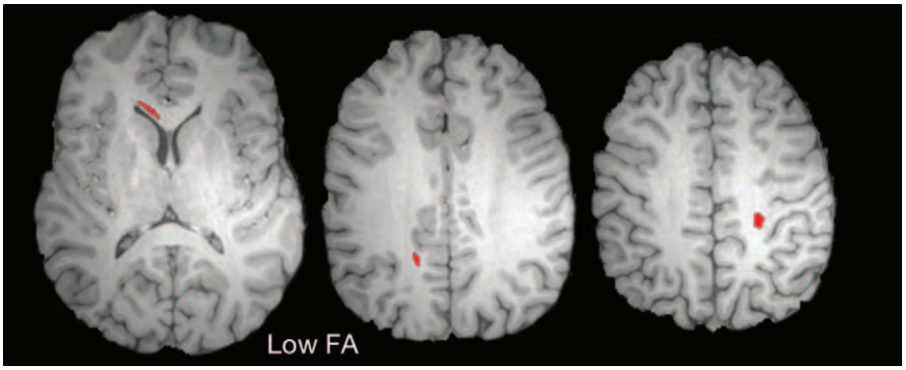

FIGURE 11. Impact of quantitative DTI on patient management, 18-year-old lacrosse player hit in front of head with a lacrosse ball, then hit in the side of the head with the ball during practice, on both occasions wearing a helmet. Two days later, he hit his forehead on a table at home, sustaining a scalp laceration. He was noted to have problems with fatigue, irritability, frustration, and poor concentration and was diagnosed with persistent postconcussion syndrome by his physician. Low FA in the deep right frontal white matter extending into the corpus callosum and the peripheral frontal white matter at the level of the centrum semiovale bilaterally, which indicates abnormality of white matter microstructure consistent with traumatic axonal injury. Findings including anterior and posterior distribution and involvement of the corpus callosum are consistent with traumatic axonal injury.

suffering persistent headache, no loss of consciousness was witnessed and he reported no posttraumatic amnesia. Initial head CT was normal, but DTI performed 8 days after the injury demonstrated abnormally low FA in the right centrum semiovale and in the splenium of the corpus callosum, consistent with acute TAI. Although this patient was on the milder end of the mTBI spectrum, quantitative analysis did demonstrate abnormality. The extent to which these manifestations of microstructural mTBI pathology will resolve, persist, or progress during the postacute period in any individual is incompletely understood and an area of active research interest.

Although specific long-term prognosis cannot, at present, be determined on the basis of the presence of acute DTI findings, the identification of abnormalities may play an important role in patient management, particularly in cases wherein the patient does not comprehend or resists the implications, clear based on clinical assessment, that a brain injury has occurred. Figure 11 shows images of an 18-year-old collegiate lacrosse player who sustained a series of 3 concussions over a period of days, approximately 7 months before MRI. Despite the absence of abnormalities on CT and standard MRI, the patient exhibited cognitive impairment and depression, which significantly reduced his capacity to complete his school work. The patient's physician diagnosed persistent postconcussion syndrome, cautioned against return to sports, and referred the patient for DTI. Quantitative analysis demonstrated low FA in deep frontal white matter extending into the corpus callosum and peripheral frontal white matter at the level of the centrum semiovale, bilaterally, consistent with TAI. The objective evidence of injury was important in counseling the patient to accept an extended medical leave from play in order to maximize his chances for recovery.

Although DTI is very sensitive, it is, like most imaging findings, not necessarily specific for TBI pathology. Special attention must be given to the clinical setting and complete patient history in order to identify or eliminate additional factors underlying the imaging findings, such as microvascular infarcts and demyelinating disease, which may result in abnormalities on DTI. Figure 12 shows a 58-year-old male with multiple vascular risk factors who presented with cognitive complaints following a motor vehicle accident after which he was diagnosed with concussion (mTBI). Extensive quantitative FA abnormalities are present, including abnormally low FA in the internal capsules, frontal white matter, right corona radiata, right occipital white matter, and splenium of the corpus callosum. Although abnormally low FA is a feature of traumatic brain injury, the patient also showed evidence of small vessel vasculopathy and chronic ischemic disease on GRE and FLAIR sequences, including microbleeds, encephalomalacia, and confluent, periventricular white matter abnormality. Although some of these types of imaging abnormalities (eg, microbleeds) may be associated with TBI, the extent and severity of gross brain pathology was out of proportion to the nature of the initial accident and clinical presentation and more likely a consequence of chronic cerebrovascular disease. Thus, the FA abnormalities found in this patient could not be specifically attributed to his recent head trauma.

CONCLUSIONS

DTI is a useful addition to the clinical assessment armamentarium applied in the setting of traumatic brain injury, as it can delineate brain abnormalities wherein conventional imaging is not revealing. It is a robust tool for use in diagnosis of acute injury, detection of injury extent, and correlation with symptoms. Optimization of acquisition parameters, careful scanner maintenance, and quality assurance are critical to the reproducibility and reliability of DTI. Currently, reasonable use of DTI follows the appropriate use of diagnostic neuroimaging in general: interpret findings in their clinical context while recognizing potential differential diagnostic possibilities, not as an absolute diagnostic or prognostic test to be used in isolation. Therefore, in the subacute and chronic settings, there is a well-defined role for DTI, as manifest clinical symptoms point to underlying microstructural abnormalities. Several examples of such use have been illustrated in this study; DTI is also capable of detecting microstructural abnormalities in the acute setting. The long-term implications of acute abnormalities, however, are still incompletely understood and remain a topic of active research. Multiple studies do demonstrate a significant association between early, quantitative DTI abnormalities and long-term outcomes,[32–36] suggesting that a role in prognostication is anticipated. Prospective identification of individuals at risk for long-term morbidity related to mTBI will allow for targeted intervention in the subpopulation likely to experience long-term deficits; currently, these individuals, who cannot be separated from the majority of patients who will recover fully, are often dismissed or lost to follow-up.

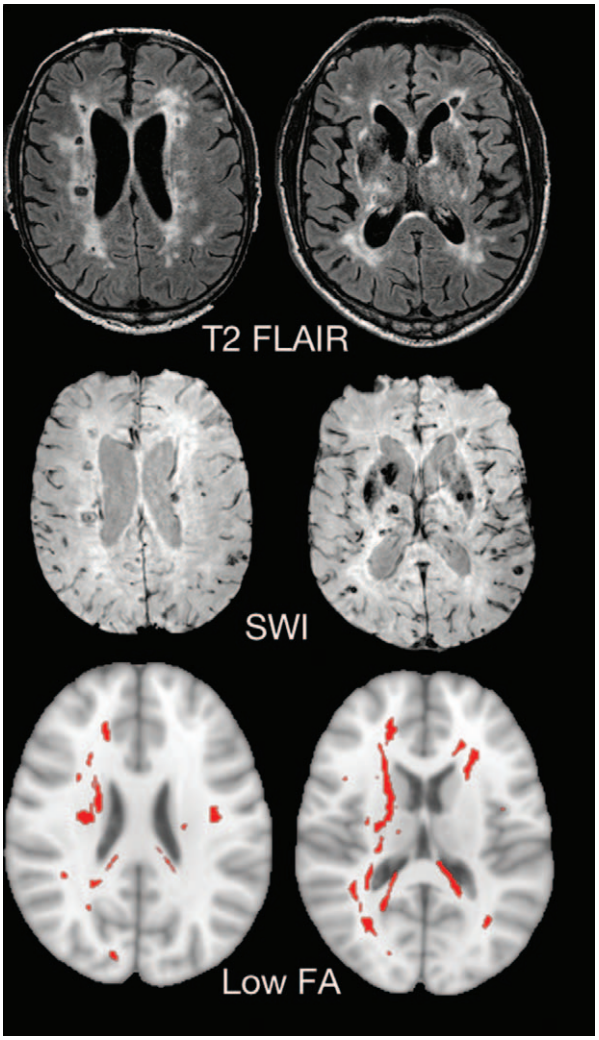

FIGURE 12. Pitfalls of quantitative DTI—vascular disease. A 58-year-old male who presents with history of TBI. Assessment of diffusion tensor imaging with quantitative analysis of fractional anisotropy (FA) demonstrates multiple areas of abnormally low FA in the internal capsules, frontal white matter bilaterally, right corona and centrum, right occipital white matter, right cerebral peduncle, and lateral aspect of the splenium of the corpus callosum bilaterally. These findings may be indicative of disruption of axonal microstructure, which is a feature of late traumatic brain injury. However, the patient also showed evidence of small vessel vasculopathy and chronic ischemic disease on SWI and FLAIR sequences, including cortical hemorrhage, encephalomalacia, and confluent, periventricular white matter abnormality, so that the FA abnormalities could not be definitely attributed to the recent head trauma.

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