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Diffusion MR Imaging in Mild Traumatic Brain Injury

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INTRODUCTION

The term “mild” in mild traumatic brain injury (mTBI) greatly understates the significance of injury when considering its major implications to patients and society. Up to 30% of patients who have suffered mTBI do not recover in the first 3 months postinjury and may suffer long-term or permanent deficits.[1,2] It is estimated that 70% to 90% of all hospital-treated head injuries are mild, with an incidence of approximately 300 in 100,000[3]; however, the true incidence is likely higher considering that many patients with mild injuries are either not treated at hospitals or not treated at all.[2,3]

Early recognition of mTBI is important because prompt medical treatment and rehabilitation are believed to improve outcome.[1] Unfortunately, standard central nervous system imaging, such as computed tomography (CT) and conventional MR imaging, has limited sensitivity for mTBI, often failing to detect brain damage despite the presence of known injury.[1,2,4] This has motivated the search for imaging biomarkers of injury in this group of patients, particularly markers that reflect patient symptoms and predict patient outcome. One of the major known forms of parenchymal injury in mTBI is axonal injury,[1] which makes advanced diffusion-weighted (DWI) MR imaging of particular interest because changes in diffusion reflect underlying changes in microstructure. Over the past decade, much has been learned regarding diffusion MR imaging, mTBI, and the use of diffusion MR imaging to detect and evaluate injury in these patients.[1,2,5]

DIFFUSION-WEIGHTED IMAGING

Restricted diffusion (ie, reduced diffusivity) on DWI can be seen in several processes, most notably cytotoxic edema, which occurs when ischemia is associated with cellular edema, typically in acute infarction.[6] There are, however, other causes of cytotoxic edema,

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particularly excitotoxic edema. Excitotoxic edema is triggered by the release of a high concentration of glutamate, which then results in intramyelinic edema, a reversible cause of cytotoxic edema. Restricted diffusion may occur acutely after white matter injury[7] (Fig. 1), although the exact mechanism is still uncertain. Some of the proposed theories for the presence of transient restricted diffusion in traumatic axonal injury include the release of glutamate from injury, resulting in excitotoxic edema[6]; the presence of associated hypoxia and hypotension, leading to trauma-induced ischemia[8]; or cytoskeletal collapse of the injured axons that would further hinder the motion of free water molecules.[9] In contrast, increased diffusivity is seen in the setting of increased extracellular water such as in with vasogenic edema.[1] Lesions from traumatic axonal injury, therefore, may show variable signal on DWI, depending on timing after injury and, because of the aforementioned mechanisms, may exhibit either increased or decreased diffusivity.[7]

Total number and volume of lesions on DWI (both with increased and decreased diffusivity) in the acute phase after head injury is shown to strongly correlate with memory deficits in mild trauma,[10] as well as with the modified Rankin Scale in moderate to severe trauma.[7] Importantly, however, although DWI has proven to detect some additional lesions not evident on T2* or fluid-attenuated inversion recovery (FLAIR), its sensitivity for lesion detection remains limited because it may not depict all of the injuries seen on other sequences.[11]

DIFFUSION TENSOR IMAGING

Diffusion tensor imaging (DTI) is a diffusion MR imaging method that measures directional diffusion of water molecules in vivo and is, therefore, of particular interest in disorders of white matter. Notably, individual axons are not resolved using DTI. Instead, the generalized diffusion properties of a white matter fiber bundle can be depicted and, with that, information about the direction and course of WM bundles can be inferred.[2] Based on this principle, DTI can indirectly reveal changes to axonal microstructure after mTBI.[12]

FRACTIONAL ANISOTROPY

The main quantitative metric derived from DTI is fractional anisotropy (FA), a measure of anisotropic diffusion.[2] Higher FA is associated with homogeneity in fiber orientation, increased fiber density or axonal diameter, and increased ratio of intracellular or extracellular space.[4] Decreased white matter FA may occur due to a variety of histopathologic changes, including damage to myelin, damage to axon membranes, reduced number of axons, decreased axonal coherence, and increased edema.

Alterations in FA have been found in patients with mTBI in both acute (time from injury <2 weeks) and chronic phases. In the chronic phase after mTBI, most reports are consistent and reveal various areas of reduced FA.[1,5,13-15] Inglese and colleagues[16] reported reduced FA in multiple areas of the brain, including corpus callosum, internal capsule, and centrum semiovale, through grouped region of interest (ROI) analysis in 26 subjects with chronic mTBI. Studies by Salmond and colleagues,[17] Kraus and colleagues,[18] and Little and colleagues[19] evaluated 16, 20, and 12 subjects with chronic mTBI, respectively.

They also found decreased FA in multiple regions of the brain using grouped voxel-based analysis, ROI, and histogram analysis. Both grouped and individual voxel-based analysis performed by Lipton and colleagues[20] on 17 subjects with chronic mTBI demonstrated similar reductions in FA.

The reported FA values in the acute phase after mTBI are variable. FA values may be increased and/or decreased.[5,13,14,16,20-27] Fig. 2 gives representative examples of the differences in FA changes reported in the literature (Fig. 3). Several metaanalyses and reviews of the literature agree that both elevated and reduced FA can be seen in subjects in the acute phase of injury after mTBI.[1,4,5,13,15] In a 2014 metaanalysis of mTBI subjects, Eierud and colleagues[13] reviewed 122 publications reporting DTI results after mTBI over the past 21 years and concluded that increased FA in the acute phase was reported more frequently than decreased FA. This could be due to a variety of reasons, including axonal injury in areas of crossing fibers and significantly reduced extracellular diffusivity in the setting of cytotoxic edema.[1] Wilde and colleagues[4] demonstrated a more complex, heterogeneous pattern of anisotropy in which FA fluctuated in the acute stage. These investigators performed serial DTI in 8 subjects with mTBI at 4 different time points within the first week after injury, noting acute transient increases of FA in the left cingulum bundle at variable time points.

Only a few longitudinal studies have been performed in subjects with mTBI.[14,27-31] These longitudinal data, though limited, corroborate the presence of variable changes in FA in brain parenchyma. Normalization, partial normalization, and worsening abnormal FA values compared with healthy controls have all been reported in longitudinal studies and may reflect tissue repair, partial tissue recovery, and continued tissue damage.[28] Mayer and colleagues[14] examined 15 healthy controls and 10 subjects in the semiacute stage after mTBI, 12 days after injury, and 3 to 5 months later. They found partial normalization of previously abnormal FA values in the splenium and corona radiata of subjects on follow-up. Arfanakis and colleagues[27] evaluated 2 subjects 24 hours after injury and 1 month after injury and found partial and complete normalization of previously decreased FA values in several white matter regions on follow-up. In a longitudinal study on mTBI, Grossman and colleagues[28] studied 16 controls and 20 subjects with mTBI 1 month and 9 months after injury and reported variable changes in different brain regions for DTI, diffusion kurtosis imaging (DKI), and arterial spin labeling (ASL) measures with time. MacDonald and colleagues[29] studied 63 subjects from military personnel with mTBI within 90 days after injury and after 6 to 12 months for follow-up. Using ROIs in grouped and individual analysis compared with controls, regions of low FA were reported in the acute phase with partial normalization on the follow-up scans. Eighteen concussed athletes within 6 days and at 6 months after injury were evaluated by Henry and colleagues[31] using grouped voxel-based analysis. They observed higher FA, higher axial diffusivity (AD), and lower mean diffusivity (MD) values in the corpus callosum and corticospinal tracts of concussed subjects in the acute and chronic setting, without significant change between acute versus chronic stages.

AXIAL AND RADIAL DIFFUSIVITY

Other metrics that can be quantified using DTI data include AD and radial diffusivity (RD). AD refers to the magnitude of diffusion along the long axis of the fiber tract, thought to be affected by pathologic processes involving axons. RD refers to the diffusivity perpendicular to the fiber tract, thought to be affected by pathologic processes involving myelin.[1,2,15] These metrics have also been explored in an effort to improve the sensitivity of DTI to mTBI. FA, MD, AD, and RD are mutually related[13]; however, AD and RD show different patterns when assessing patients with traumatic brain injury (TBI) in terms of time since injury and severity of injury.[15] According to the current literature,[14,25] in the acute and subacute phase of mTBI, AD seems to remain comparable to that of controls, whereas RD has been reported to be both elevated[25] and reduced.[14] In the study by Kumar and colleagues,[25] elevated RD values were observed in the genu and splenium of 26 subjects with mTBI compared with 33 healthy controls, using ROI analysis in the acute period (within 5–14 days) after injury. In contrast, Mayer and colleagues[14] observed low RD in the genu and several left hemispheric white matter tracts in 22 subjects with mTBI, using ROI analysis during the acute to subacute stages of trauma (within 21 days, mean of 12).

In the chronic phase after injury, Kraus and colleagues[18] found elevated AD values throughout all severities of trauma, whereas RD changes seemed to depend on injury severity. The investigators found no significant difference in RD in 20 subjects with mild chronic injury when compared with controls but higher RD in chronic moderate or severe TBI. These differences in RD are likely due to the intrinsic diversity of neuroinflammatory mechanisms in TBI[15] and possibly irreparable damage to myelin with greater degrees of injury.

DIFFUSION KURTOSIS IMAGING

The model used for DTI at typical maximal b-values of 1000 s/mm^2 is based on assuming a Gaussian distribution of diffusion. At higher b-values, however, diffusion displacement in white matter is known to be non-Gaussian. DKI uses multishell imaging with multiple b-values beyond 1000 to quantify this non-Gaussian behavior (Fig. 4).[32,33] Kurtosis is a measure of the deviation from a Gaussian distribution and is a measure of tissue microstructural complexity.[2,34] Thus, DKI has theoretic advantages in detecting subtle injury in tissue and may be of specific utility in areas normally shown to have relatively low FA in which the potential of DTI metrics to detect injury may be lower.

DKI results in the literature are consistent with DTI findings in longitudinal studies and may provide additional information about DTI.[28,35] In a longitudinal study by Grossman and colleagues,[28] 20 subjects with mTBI demonstrated significant differences from 16 controls in DTI, DKI, and ASL measures in the thalamus and white matter within 1 month and 9 months after injury, correlating with cognitive performance. Fig. 5, reprinted from this longitudinal study, illustrates differences in mean kurtosis (MK) in the thalamus of impaired and unimpaired subjects with mTBI compared with controls. Results show that impaired subjects with TBI had lower MK values than unimpaired subjects and controls (see Fig. 5). Reduced MK and radial kurtosis but no significant changes in DTI were reported in the

anterior internal capsule of 24 subjects with mTBI when examined in a longitudinal study by Stokum and colleagues[35] at 10 days, 1 month, and 6 months postinjury. Improvements in cognition 1 to 6 months after injury correlated with changes in MK and radial kurtosis in the thalamus, internal capsule, and corpus callosum. Lancaster and colleagues[36] performed DTI and DKI in 26 high school and college athletes with sports-related concussion within 24 hours from injury and at 8 days. They found higher axial kurtosis in the corpus callosum and several white matter tracts in subjects compared with controls, which also positively correlated with symptoms.

INJURY LOCALIZATION

Despite variations in methodology, group analysis with DTI points to several specific anatomic regions of frequent injury in mTBI,[13] suggesting vulnerability of these areas.[2] Frequently reported areas of white matter injury include frontal lobe, corpus callosum, posterior limb of internal capsule, cingulum, and fronto-occipital fasciculus.[5,37] In addition to white matter injury, thalamic injury has been described in mTBI.[19,37] Although this information is applicable for group analyses, reliably detecting specific areas of injury in individual subjects remains a work in progress.[38]

DIFFUSION TRACTOGRAPHY

Diffusion tractography relates diffusion profiles across voxels and reconstructs structural diffusion pathways in the brain corresponding to major visualized white matter fiber bundles.

Limitations include lack of standardization of tractography algorithms and potential low sensitivity for detecting small lesions.[15,39] Deterministic tractography, currently among the most popular methods of tractography available on vendor platforms, does not account for crossing fibers and tracts that have broad, multidimensional direction.[2] Research efforts to solve these problems include high angular resolution diffusion imaging (HARDI) and diffusion spectrum imaging (DSI).[1,15]

DIFFUSION AND COGNITION

Conventional imaging findings in mTBI do not correlate with neurocognitive performance. In contradistinction, the global burden of disease in mTBI measured by DTI (ie, number of DTI lesions detected or average FA over multiple ROIs) is reported to correlate with executive function and cognitive processing speed.[15] Miles and colleagues[26] studied 17 subjects with mTBI and found a positive correlation between low FA and poor executive function, as measured in the Prioritization Form B test. Results from a study of Niogi and colleagues[40] of 34 subjects with mTBI suggest negative correlation between overall number of DTI lesions (defined as FA <2.5 SD from the average in a set of predetermined ROIs) and the mean reaction time in the cognitive tasks performed (attention network task).

In addition to global burden of injury, current literature suggests that injuries in specific areas of the brain, such as frontal white matter, correlate with poor attention, memory, learning, and executive function.[13,28,41] Lipton and colleagues[41] reported a positive

correlation between low FA in the frontal white matter and poor performance on tests of executive function (continuous performance task and the executive maze task) in 34 subjects with mTBI studied 2 to 14 days after the trauma. There is an increasing body of literature associating alterations of thalamic diffusion with altered neuropsychological studies in mTBI.[37] Little and colleagues[19] found a correlation between low thalamic FA and lower scores on neurocognitive tests of attention, memory, and executive function performed in 12 subjects with mTBI within 12 months from the injury. A DKI study performed by Grossman and colleagues[37] evaluating 20 subjects with mTBI, also demonstrated lower MK and FA in the thalamus and internal capsule of subjects with cognitive impairment compared with subjects without cognitive impairment, within and after 1 year from mild trauma.

Altered performance in neuropsychological tests may variably correlate with FA values. In a metaanalysis of mTBI, Eierud and colleagues[13] found poor neuropsychological performance correlated with high FA in the acute phase and low FA in the chronic phase. Others; for example, Wilde and colleagues,[4] studied 8 subjects with mTBI within 8 days postinjury and found inconsistent correlation between FA values and performance on memory tasks. The pattern of FA was variable (sometimes transiently elevated), independent of the task performance.

SPECIAL POPULATIONS: PEDIATRIC PATIENTS

Children, age 0 to 4 years, and adolescents, age 15 to 19, are at high risk for TBI,[28,42] though they are less likely to report postconcussive symptoms and have better outcomes than older patients, possibly due to greater neuroplasticity.[43,44] Despite being a high-risk group for head injury, few studies specifically address the pediatric population.[21,24,45] The available studies mirror some of the results derived from adult data with elevated FA, decreased MD, and decreased RD in the acute phase involving corpus callosum and cingulum bundle.[21,24,45]

Changes in FA and RD in adolescents with mTBI have also been reported to correlate with both performance on neuropsychological tests and postconcussive symptoms.[21,45] A DTI study by Wu and colleagues[45] on 12 adolescents (range 14–17 years) 1 to 6 days post-mTBI showed a correlation between high FA in the left cingulum bundle with poor episodic verbal learning and memory task. Wilde and colleagues[21] performed DTI in the corpus callosum of 10 adolescents with mTBI 1 to 6 days after trauma and found that increased FA and decreased RD in the corpus callosum correlates with the severity of postconcussion symptoms. High FA in the frontal and supracallosal white matter was also found in the chronic stage of mTBI 6 to 12 months postinjury in 24 subjects of ages 10 to 18 years, compared with 24 controls in a study performed by Wozniak and colleagues.[46]

To the authors' knowledge, there are no current published studies using DKI in pediatric patients with mTBI.

SEX DIFFERENCES

The impact of sex and progesterone on TBI risk, severity, and outcome remains a controversy, in view of the limited literature and conflicting results. Several studies using

neuropsychological testing and symptom scale questionnaires[44,47-49] suggest women may have worse outcome compared with men. Contrary to some of the existing literature, a DTI study of mTBI subjects by Fakhran and colleagues[50] concluded that male sex was an independent risk factor for persistent postconcussive symptoms at 3 months after injury. In addition, a Cochrane review of the literature, including 8 studies that investigated the effects of progesterone in TBI, did not find sufficient evidence to prove that progesterone could reduce mortality or disability in subjects with TBI.[51]

ONGOING RESEARCH

Creation of a normative atlas is considered a fundamental step in the future of mTBI imaging research, which would allow the establishment of normative values and an accurate comparison between subjects and healthy subjects.[12]

Efforts are underway to pursue larger, multicenter trials with standardized methodology. The National Institute of Neurologic Disorders and Stroke (NINDS)-funded, multicenter Transforming Research and Clinical Knowledge in Traumatic Brain Injury (TRACK-TBI) study aims to collect and analyze detailed clinical data on 3000 subjects at 11 US sites, across the injury spectrum, along with CT or MR imaging, blood biospecimens, and detailed clinical outcomes (https://tracktbi.ucsf.edu). The TRACK-TBI Pilot dataset is the first to populate the Federal Interagency Traumatic Brain Injury Research (FITBIR) repository and, with the current TRACK-TBI data, is compatible with the International Initiative for Traumatic Brain Injury Research (InTBIR), a collaborative effort of the European Commission (EC), the Canadian Institutes of Health Research (CIHR) and the National Institutes of Health (NIH). The Federal Interagency TBI Research (FITBIR) Informatics System (https://fitbir.nih.gov/) is the result of a collaboration that began in 2011 between the NIH and the US Department of Defense. Its purpose is to create a national resource for archiving and sharing clinical data from research studies on TBI, along with appropriate control data.[38]

Efforts to improve sensitivity and specificity of diffusion MR imaging for detecting injury in mTBI[12] are ongoing. Promising technical developments are being made on acquisition and postprocessing, as well as modeling. Multidimensional, multishell acquisitions, such as HARDI and DSI, allow for resolution of crossing fibers by measuring intravoxel diffusion in multiple directions.[52] Multitensor models allow tracing of small, peripheral fiber bundles.[53] Track-density imaging is a postprocessing technique using super resolution to obtain intravoxel information derived by whole-brain probabilistic streamline tractography.[54] This allows for visualization of smaller pathways that are typically not identified using conventional DTI and can work toward solving the problem of crossing fibers (Fig. 6).[55]

Newer, quantitative analyses use compartment-specific modeling of diffusion in both intracellular and extracellular spaces. This allows the derivation of modeled metrics believed to have greater biophysical meaning than traditional empirical DTI and DKI metrics. Such modeled metrics include axonal water fraction (a marker of axon density),[56] intraaxonal diffusivity (a marker of intra-axonal injury),[57] extraaxonal axial and radial diffusivities (eg, markers of changes in extraaxonal space associated with gliosis, astrocytosis, extracellular

inflammation), and extraaxonal tortuosity (a marker of myelination or alignment of fibers).[58] Extraaxonal RD would also be sensitive to demyelination.[56] These newer metrics provide more information beyond the traditional empiric diffusion metrics such as FA.

SUMMARY

Remarkable advances have been made in the last decade in the use of diffusion MR imaging to study mTBI.[1,2,5,13] Diffusion shows differences between mTBI subjects and healthy control groups in multiple different metrics using a variety of techniques, supporting the notion that there are microstructural injuries in mTBI patients that radiologists have previously been insensitive to.

Important future areas of discovery in diffusion MR imaging and mTBI include larger longitudinal studies to improve the understanding of the evolution of injury after mTBI and unravel the biophysical meaning of what detected changes in diffusion MR imaging may represent.

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KEY POINTS

- Advanced diffusion-weighted MR imaging is of particular interest in the study of mild traumatic brain injury because changes in diffusion reflect underlying changes in microstructure.
- Diffusion-weighted imaging, diffusion tensor imaging, and diffusion kurtosis imaging can reveal alterations in the brain parenchyma in acute and chronic mTBI that are not identified with standard central nervous system imaging.
- Specific areas of the brain have shown vulnerability to damage after mild injury and may correlate with altered cognitive performance.
- Promising technical developments are being made and efforts are underway to pursue larger, multicenter trials with standardized methodology to better understand what detected changes in diffusion MR imaging represent.

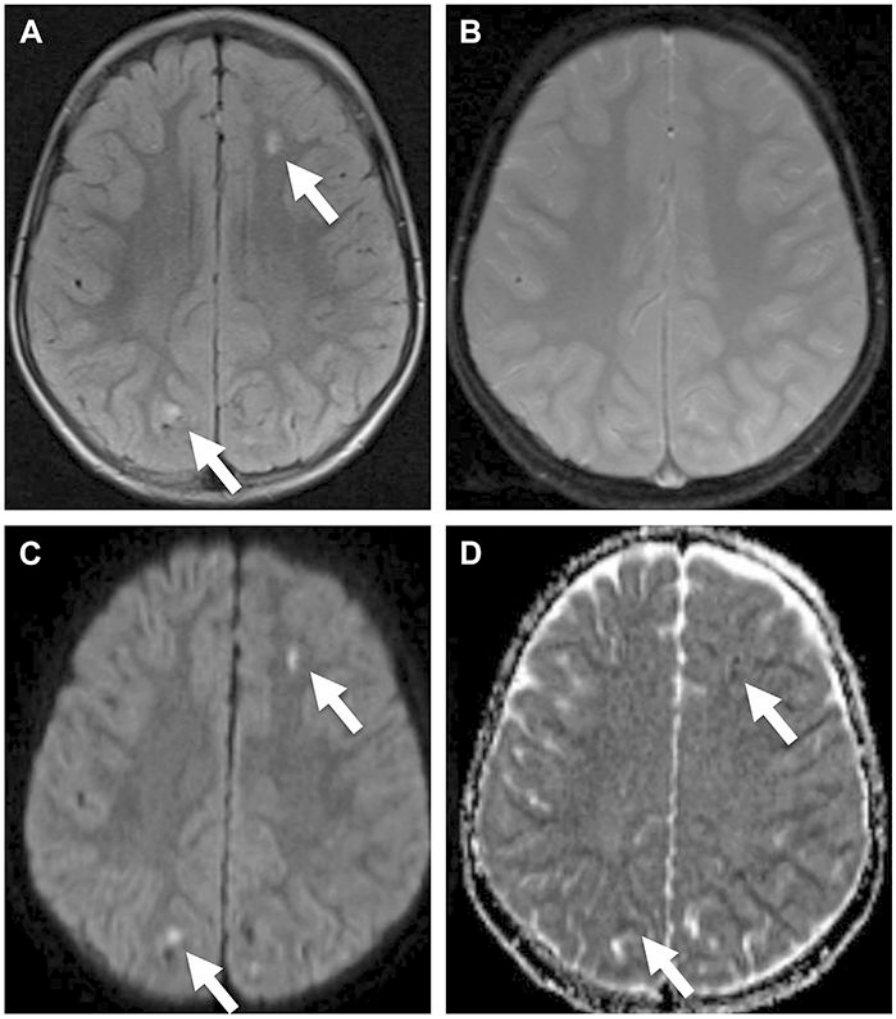

Fig. 1.

A 5-year-old boy with traumatic axonal injury at the level of the centrum semiovale. The lesions (*arrows*) are hyperintense on fluid-attenuated inversion recovery (FLAIR) (*A*), do not demonstrate appreciate susceptibility on T2*-weighted images (*B*), and show restricted diffusion on DWI (*C*) and apparent diffusion coefficient maps (*D*), reflecting acute injury.

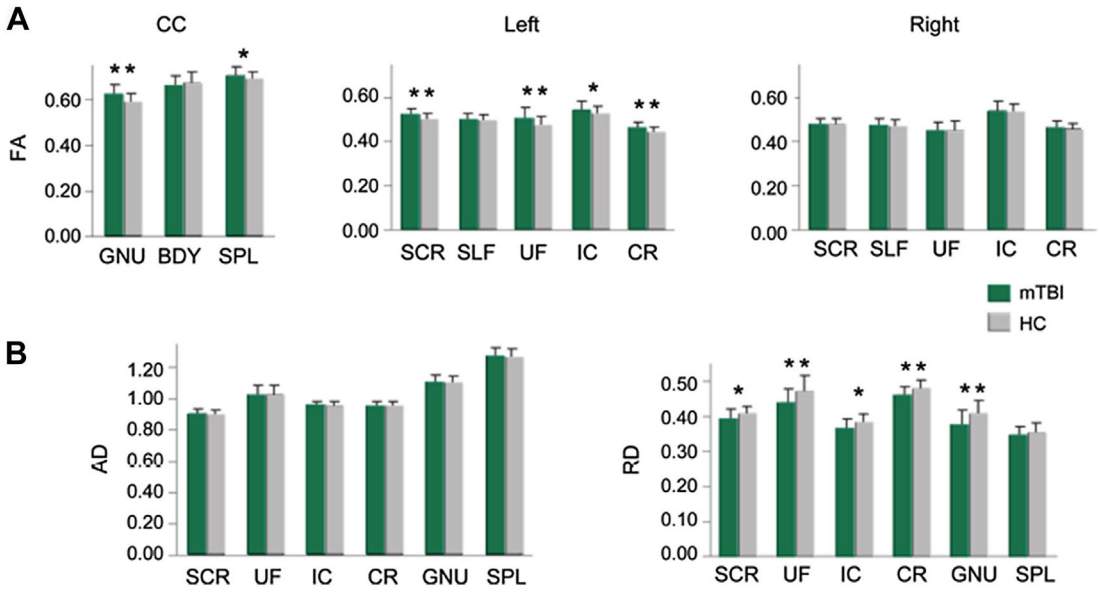

Fig. 2.

Mean FA values (*A*) from ROI in the genu (GNU), body (BDY), and splenium (SPL) of the corpus callosum (CC), superior corona radiata (SCR), superior longitudinal fasciculus (SLF), uncinate fasciculus (UF), corona radiata (CR), and internal capsule (IC). Patients with mTBI (*green bars*) showed mostly higher FA values than healthy controls (*gray bars*). Significance is indicated with double asterisks, statistical trends with single asterisk. Axial diffusivity and radial diffusivity (*B*) measurements from mTBI patients and healthy controls for regions with statistical differences in FA. (*From* Mayer AR, Ling J, Mannell MV, et al. A prospective diffusion tensor imaging study in mild traumatic brain injury. Neurology 2010;74(8):643–50; with permission.)

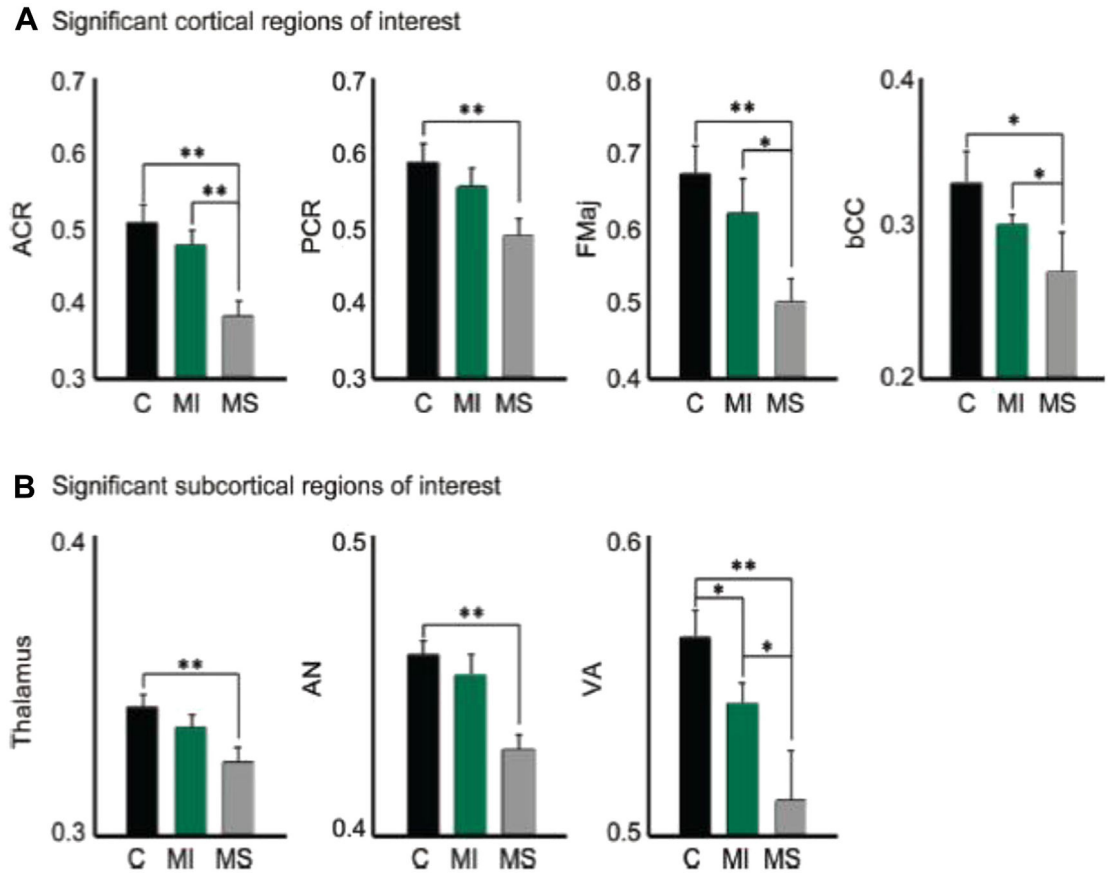

Fig. 3.

Mean FA extracted from the (*A*) anterior corona radiata (ACR), posterior corona radiata (PCR), forceps major (fMaj), and body of the corpus callosum (bCC), as well as from the (*B*) thalamus, anterior thalamic nucleus (AN) and ventral anterior thalamic nucleus (VA). Patients with mTBI (MI) showed lower FA than controls (C), but higher than moderate/severe TBI (MS). Significance is indicated (**P* = .05; ***P* = .01). (*From* Little DM, Kraus MF, Joseph J, et al. Thalamic integrity underlies executive dysfunction in traumatic brain injury. Neurology 2010;74(7):558–64; with permission.)

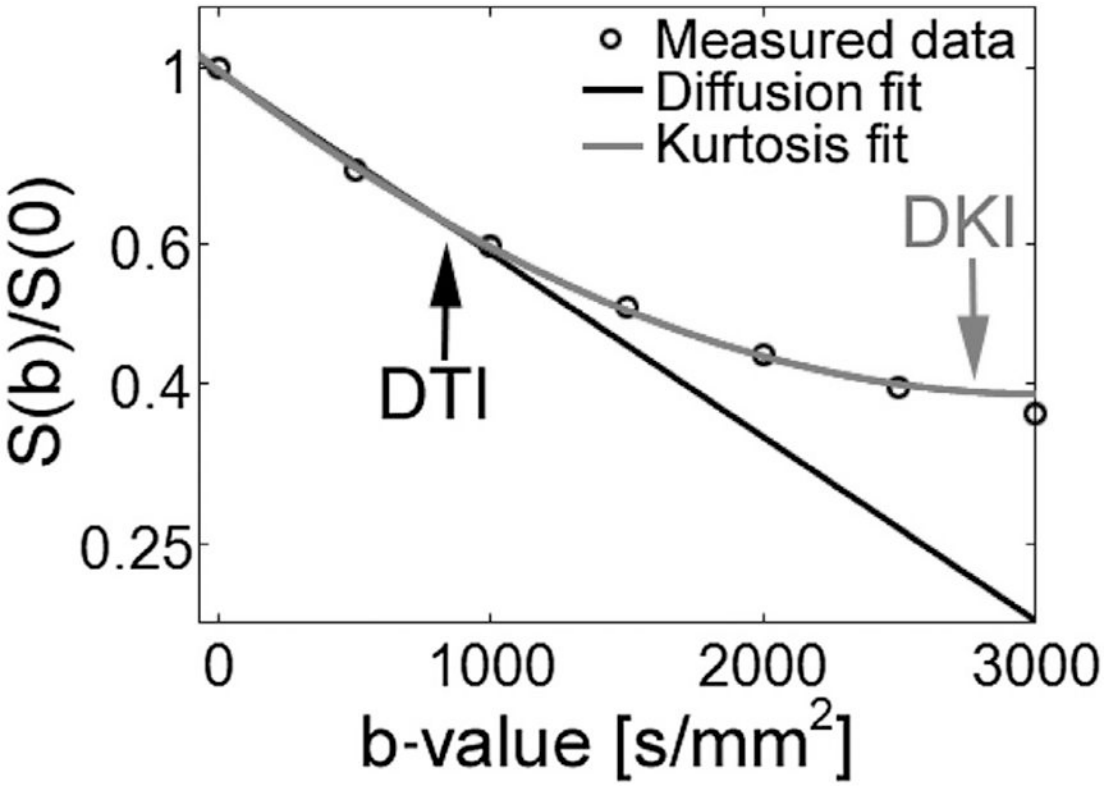

Fig. 4.

Signal intensity versus diffusion b-value. Graph of signal intensity against diffusion b-value demonstrating improved modeling of DKI compared with DTI at higher b-values. S(b)/S(0), normalized signal.

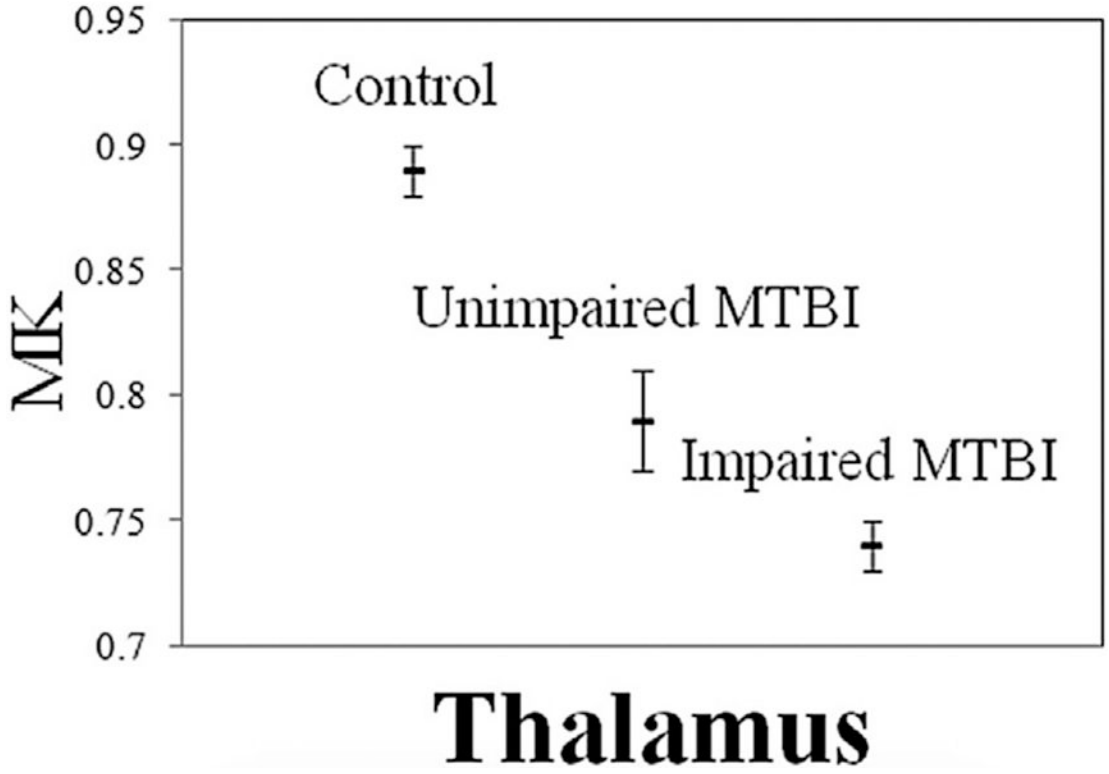

Fig. 5.

Mean (*hash marks*) and standard error (*lines*) for thalamic mean kurtosis (MK) in controls, and for cognitively normal and cognitively impaired subjects. Cognitively impaired subjects show significantly lower MK in the thalamus than unimpaired subjects and controls. (*From* Grossman EJ, Jensen JH, Babb JS, et al. Cognitive impairment in mild traumatic brain injury: a longitudinal diffusional kurtosis and perfusion imaging study. AJNR Am J Neuroradiol 2013;34(5):951–7, 955; with permission.)

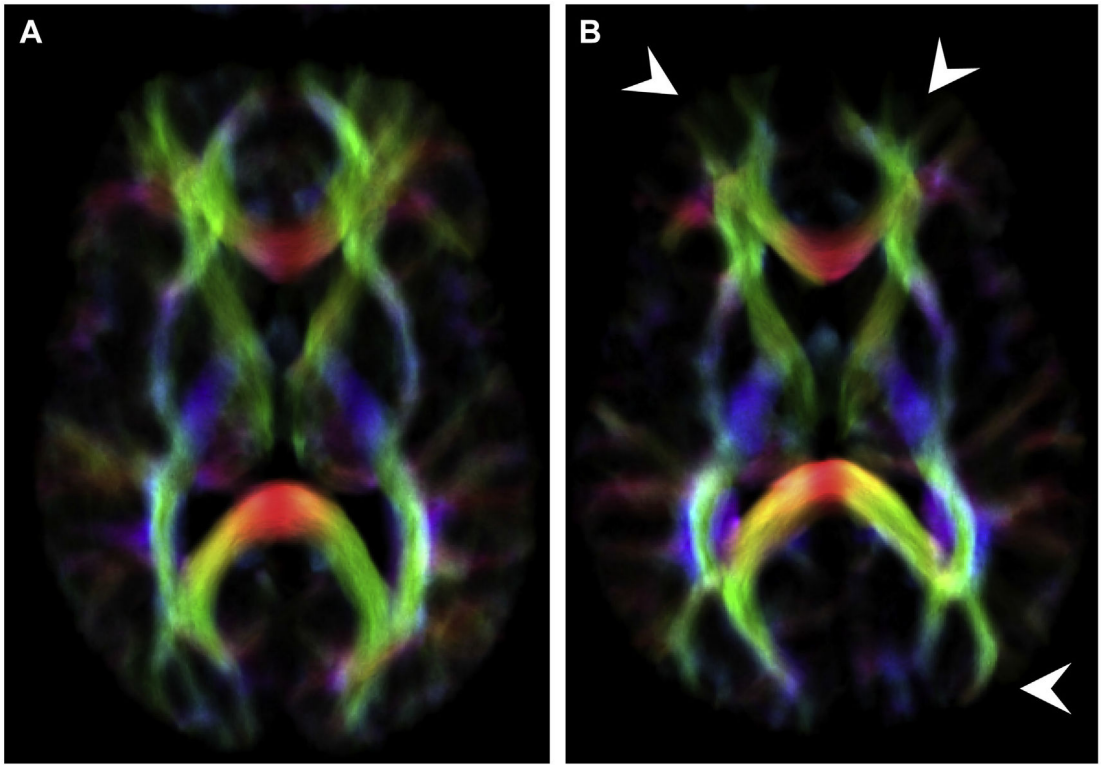

Fig. 6.

Directionally encoded color track-density imaging maps in a 37-year-old man with mTBI (*B*) and a healthy control matched for age and sex (*A*) show global relative paucity of peripheral tracts extending to the subcortical region (*arrowheads*) compared with the healthy control.