JOURNAL OF NEUROTRAUMA 25:1335–1342 (November 2008)

DOI: 10.1089/neu.2008.0547

Multifocal White Matter Ultrastructural Abnormalities in Mild Traumatic Brain Injury with Cognitive Disability: A Voxel-Wise Analysis of Diffusion Tensor Imaging

Michael L. Lipton,[1,2,4] Erik Gellella,[1] Calvin Lo,[1] Tamar Gold,[1] Babak A. Ardekani,[4] Keivan Shifteh,[1] Jacqueline A. Bello,[1] and Craig A. Branch[1,3,4]

Abstract

The purpose of the present study is to identify otherwise occult white matter abnormalities in patients suffering persistent cognitive impairment due to mild traumatic brain injury (TBI). The study had Institutional Review Board (IRB) approval, included informed consent and complied with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. We retrospectively analyzed diffusion tensor MRI (DTI) of 17 patients (nine women, eight men; age range 26–70 years) who had cognitive impairment due to mild TBI that occurred 8 months to 3 years prior to imaging. Comparison was made to 10 healthy controls. Fractional anisotropy (FA) and mean diffusivity (MD) images derived from DTI (1.5 T; 25 directions; b = 1000) were compared using whole brain histogram and voxel-wise analyses. Histograms of white matter FA show an overall shift toward lower FA in patients. Areas of significantly decreased FA ($p < 0.005$) were found in the subject group in corpus callosum, subcortical white matter, and internal capsules bilaterally. Co-located elevation of mean diffusivity (MD) was found in the patients within each region. Similar, though less extensive, findings were demonstrated in each individual patient. Multiple foci of low white matter FA and high MD are present in cognitively impaired mild TBI patients, with a distribution that conforms to that of diffuse axonal injury. Evaluation of single subjects also reveals foci of low FA, suggesting that DTI may ultimately be useful for clinical evaluation of individual patients.

Key words: cognitive impairment; diffusion tensor imaging; magnetic resonance imaging; mild traumatic brain injury

Introduction

Traumatic brain injury (TBI) is a major public health problem, affecting more than 1.4 million Americans each year with 2% of the U.S. population (5.3 million persons) disabled due to TBI (McArthur et al., 2004). While the devastating consequences of severe TBI are well-known, long-term effects of mild injury also have substantial personal and societal impact (Weight, 1998; Holm, 2005; Gamboa et al., 2006). Direct and indirect costs of TBI exceed $80 billion annually in the United States (CDC, 2003).

Following mild TBI (mTBI), patients may complain of an array of symptoms, including headache and impaired concentration and memory (Kushner, 1998). Because symptoms are mild and nonspecific, patients may not seek medical treatment or be seen only briefly and released (Kushner, 1998). Computed tomography (CT) or magnetic resonance imaging (MRI) is commonly normal (Inglese et al., 2005), if it is performed at all. Recovery may occur over months. However, up to 30% of mTBI patients will suffer permanent sequelae of their injury and up to 20% will be unable to return to work (Nolin and Heroux, 2006).

Conventional CT and MRI are quite insensitive to mTBI pathology, likely due to the small size and subtle nature of mTBI lesions (Gentry et al., 1988; Kelly et al., 1988; Arfanakis et al., 2002; Huisman et al., 2004); frank tissue disruption does not necessarily occur (Huisman et al., 2003). Hemorrhage may be a sentinel marker for TBI lesions (Kushner, 1998), but is uncommon in mTBI (Huisman et al., 2003). The full extent of lesions may not manifest initially, no matter what means

Departments of [1]Radiology, [2]Psychiatry and Behavioral Sciences, and [3]Neuroscience, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York.
[4]Center for Advanced Brain Imaging, The Nathan S. Kline Institute for Psychiatric Research, Orangeburg, New York.

are used for detection, because TBI lesions evolve over time due to a cascade of cellular events (Nortje and Menon, 2004).

Diffusion tensor MRI (DTI) shows lower fractional anisotropy (FA) in TBI patients that may correlate with disability (Ptak et al., 2003; Huisman et al., 2004). Two reports described DTI in TBI patients with cognitive impairment (Ewing-Cobbs et al., 2006; Nakayama et al., 2006). However, these and most studies of DTI in TBI have examined patients close to the time of injury (Arfanakis et al., 2002; Ptak et al., 2003; Huisman et al., 2004), and with moderate to severe TBI (Wieshmann et al., 1999; Rugg-Gunn et al., 2001; Huisman et al., 2004; Nakayama et al., 2006; Tisserand et al., 2006). Even in studies of "mTBI," reported brain hemorrhage in the study subjects suggests that more severe injury may have occurred (Arfanakis et al., 2002; Inglese et al., 2005). A recent report on mTBI included a subgroup with remote injury, but did not address cognitive impairment (Inglese et al., 2005). In addition to lower FA, higher mean diffusivity (MD) is characteristic of TBI lesions, likely due to loss of tissue structure that would otherwise impede free diffusion (Inglese et al., 2005).

The purpose of the present study is to identify otherwise occult white matter abnormalities in patients suffering persistent cognitive impairment due to mTBI. We hypothesized that lower FA and higher MD than in healthy normal controls, indicating disorganization of white matter microstructure due to injury, are features of the brains of patients suffering cognitive impairment as a functional consequence of mTBI.

Material and Methods

Study subjects

All aspects of the study were Institutional Review Board (IRB) approved and U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996 compliant. The IRB provided a waiver of informed consent for our retrospective review of the patient data. Control subjects gave informed consent for their participation.

TBI patients. We retrospectively analyzed DTI in seventeen consecutive mTBI patients (nine women, eight men; age range 26–70 years) who met inclusion and exclusion criteria (six patients were excluded due to imaging evidence of hemorrhage or comorbid conditions). All patients had suffered a mild head injury to which no significant clinical sequelae were initially ascribed. In each case, the patient later (8 months to 3 years following injury) sought medical evaluation due to symptoms including difficulty with attention, concentration, memory and job performance. As part of their clinical evaluation, patients were referred for MRI to exclude structural brain abnormalities as a cause of their symptoms. DTI was routinely included in brain imaging studies at this time, affording the opportunity to retrospectively assess DTI in this population. Patient data (excluding imaging) was derived from referring clinic records including clinical neuropsychological reports. Inclusion criteria were as follows: (1) witnessed closed head trauma (motor vehicle accidents [$n = 15$], falls [$n = 1$], struck by construction debris [$n = 1$]); (2) initial evaluation at a clinic or emergency room with findings consistent with mTBI (Glasgow Coma Scale [GCS] score [if available] of 13–15, loss of consciousness for less than 20 min, post-traumatic amnesia of less than 24 h, no other neurological deficit); and (3) persistent cognitive deficits due to TBI diagnosed by a neuropsychologist during the clinical evaluation of the patient's symptoms. Exclusion criteria were as follows: (1) hospitalization due to the injury; (2) abnormal brain imaging at the time of injury; (3) history of other prior head trauma; (4) pre-injury cognitive impairment; (5) other neurological or psychiatric disease; and (6) substance abuse.

Control subjects. Ten control subjects of similar age and gender distribution to the patient group were recruited and underwent the same imaging protocol on the same scanner as the patients. Similarity of the group demographics was confirmed using χ^2 (gender) and Student's t-test (age). Control exclusion criteria were as follows: (1) history of head injury; (2) history of neurological or psychiatric disease; or (3) history of substance abuse.

Imaging protocol

Imaging was performed on a 1.5-Tesla Signa Excite MR/i scanner (General Electric, Waukesha, WI) with Echospeed+ gradients and transmit-receive birdcage head coil. Whole head structural imaging included sagittal 3D-FSPGR (TR 7.6 msec, TE 1.6 msec, two signal averages, 30º flip angle, and 0.6-mm isotropic resolution) and axial FSE-XL (TR 3155 msec, TE 104 msec, two signal averages, echo train 17, 23 × 23 cm FOV, 512 × 224 matrix, 5-mm section thickness). DTI was acquired using single shot EPI at 5-mm slice thickness, FOV = 260 mm, 128 × 128 matrix, 25 diffusion sensitizing directions, and b = 1000 s/mm^2. DWI images were corrected for eddy current effects, and FA and MD images were calculated automatically using a console-based algorithm. Axial FLAIR (TR 800 msec, TE 120 msec, one signal average, TI 2250 msec, FOV 22 × 22 cm, 256 × 224 matrix, 5 mm slices) and axial GRE (TR 750 msec, TE 17 msec, two signal averages, 15° flip angle, FOV 22 × 22 cm, 256 × 192 imaging matrix, 5-mm slices) images were also obtained.

Data and statistical analysis

Two American Board of Radiology certified neuroradiologists independently reviewed brain images for structural abnormalities including assessment for evidence of hemorrhage. Any disagreement in interpretation was resolved by consensus.

Quantitative image analysis was performed offline as discussed next.

Whole brain histogram analysis. Individual 256-bin histograms were generated from each subjects whole-brain FA dataset, after skull stripping (using a unique brain mask for each subject, derived from that subject's B = 0 image), but prior to any image manipulation. Total number of brain voxels and kurtosis was computed separately for each subject's histogram. Subject and control histograms were compared between groups using Student's t-test and were then group-averaged for display.

Voxel-wise analysis.

- **Skull stripping:** Non-brain voxels were removed from the FSPGR and FSE images using Functional Magnetic Reso-

nance Imaging of the Brain (FSL) software (Smith et al., 2004). Each brain volume was inspected slice-by-slice, and residual non-brain voxels were removed manually.

- **EPI distortion correction:** FSE images were acquired with identical slice position and orientation as DTI. Distortion correction was accomplished using two-dimensional (2D) nonlinear deformation algorithm to match eddy current-corrected EPI to FSE volumes (Lim et al., 2006).
- **Intermediate rigid-body registration:** Each subject's FSE images were registered to their three-dimensional (3D) FSPGR images using the Automated Registration Toolbox (ART) (Ardekani, 1995) 3D rigid-body approach (Ardekani et al., 2005).
- **Registration to standard space:** The 3D nonlinear registration module of ART registered each subject's 3D FSPGR volume to a standard T1-weighted template (Montreal Neurological Institute [MNI] atlas).
- **Transformation of DTI images to standard space:** Using ART, distortion correction, intermediate rigid-body registration, and standard space registration (above) were applied to the calculated FA and MD maps using a single reslicing operation. Final cubic voxel size was 1 mm^3, masked to exclude non-brain voxels from the analysis (above).
- **Segmentation:** The fast automated segmentation tool (FAST) within FSL was used to generate a white matter mask for the template brain. This mask was eroded by 3 pixels to limit edge effects and was used to restrict subsequent statistical analysis of FA to white matter voxels.
- **Voxel-wise statistical analysis (VSA)**: ART was used to perform a *t*-test separately comparing patient vs. control FA and MD at each voxel, covarying for age and gender. Type I errors (false positives) were controlled using the false discovery rate (FDR) measure in FSL (Benjamini and Hochberg, 1995). FDR is the expected proportion of rejected hypotheses that are false positives. FDR = 0.01 corresponded to $p = 0.0071968$. Thus, we selected a *p*-value threshold of 0.005 for our analyses to ensure an FDR of <0.01 (1%). As an additional safeguard against false positives, we only retained clusters of size greater than 100 voxels (100 mm^3).
- **Statistical images:** Those images representing significant group differences are displayed as color overlays superimposed on T1-weighted images from the MNI template.

Results

The patient and control populations did not differ with respect to age ($p = 0.58$) or gender ($p = 0.91$). Neuropsychological deficits found in the patient population included memory, executive function, attention, mood and affect. Any imaging performed at the time of injury was normal based on records, but the images were not available for review.

No evidence of hemorrhage was found on review of images. A small area of signal abnormality attributed to gliosis was found in one subject. No other structural abnormalities were detected. Assessments of both reviewers were concordant in all cases.

The histogram (Fig. 1) of whole brain FA from patients reveals a significantly smaller number of brain voxels than in controls ($p = 0.004$). For this reason, we scaled the histograms to correct for the volume difference. Both before and after scaling, the patient histogram is shifted to the left with respect to controls and the greatest group difference appears to be at highest FA. Comparison of the kurtosis of patient and control histograms (prior to scaling) confirms that histograms are significantly different ($p = 0.006$), indicating a small, but significant difference in whole brain FA; while most brain voxels express similar FA in patients and controls, a subset of voxels in the patient group have lower FA than controls.

Voxel-wise analysis detected multiple clusters of lower FA ($p < 0.005$) bilaterally in the white matter of patients compared to controls (Fig. 2). Affected areas include corpus cal-

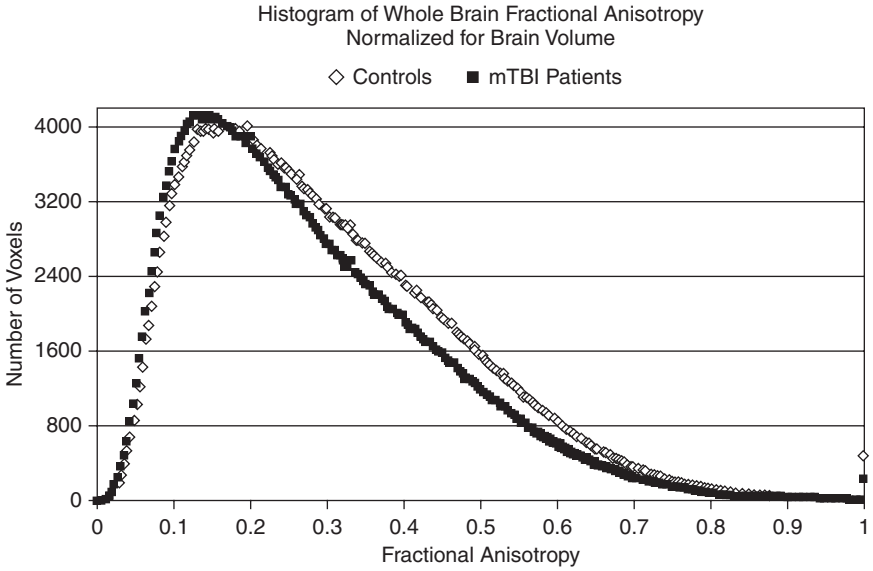

FIG. 1. Histogram of white matter ractional anisotropy (FA) corrected for brain volume. The FA histogram for patients (black) is shifted to the left with respect to controls (gray). This pattern suggests that a subset of voxels in the patient group has lower FA, as detected in subsequent voxel-wise and region of interest (ROI) analyses.

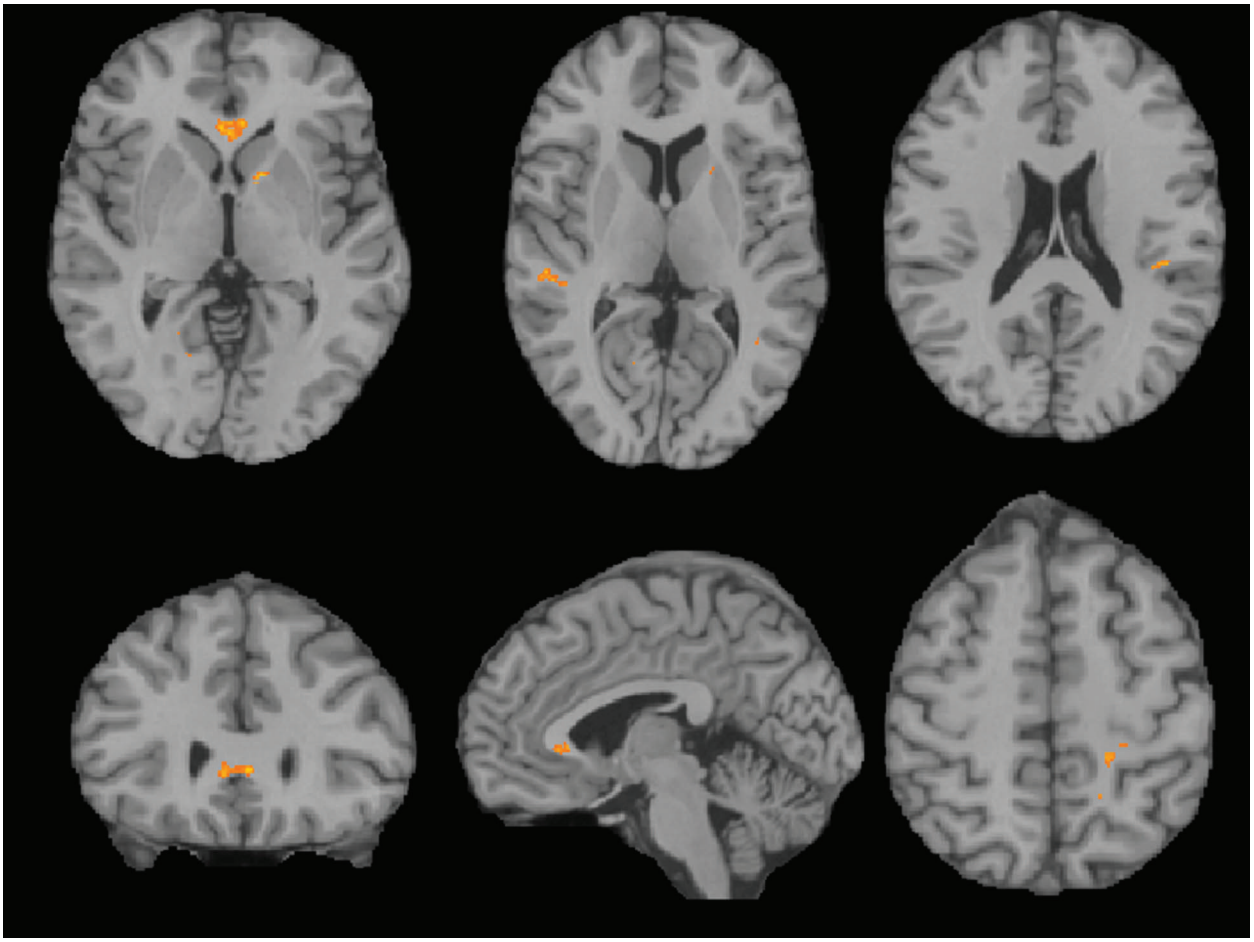

FIG. 2. Voxel-wise analysis comparing fractional anisotropy (FA) in patients and controls. Colored regions superimposed on structural images (axial, top row and lower right; coronal, lower left and sagittal, lower center) from the Montreal Neurological Institute (MNI) template indicate some locations found to have significantly lower FA in patients. Multiple abnormalities are present in deep and subcortical white matter, a pattern similar to that found in diffuse axonal injury (DAI).

losum, internal capsules, subcortical white matter, centrum semiovale and deep cerebellar white matter (not all shown), but not the brainstem. Significantly lower FA (Table 1) and higher MD (Table 2) are present in patients compared to controls in each cluster.

Comparison of FA values from individual TBI subjects with those from the entire control group showed similar, although less robust decreases of FA in each case. The results from one subject are shown in Figure 3. No evidence of pathology is present in FLAIR and GRE images, nor is evidence of the FA deficit clearly visible in the individual subject's FA map. Findings in other subjects were similar.

Discussion

DTI was used to identify white matter abnormalities in patients with persistent cognitive impairment following mTBI. While other studies have reported diffusion abnormalities in

TABLE 1. FA (MEAN ± STANDARD DEVIATION) FOR MTBI PATIENTS AND CONTROLS (*T*-TEST, 2-TAILED)

Region	*MNI coordinates*	*Subjects*	*Controls*	p-*value*
Right orbitofrontal	(75.76, 54.82, 58.11)	0.376 ± 0.052	0.497 ± 0.056	0.00000629
Right anterior limb of internal capsule	(76.45, 81.63, 70.82)	0.463 ± 0.061	0.605 ± 0.036	0.000000534
Corpus callosum genu	(88.67, 63.32, 71.88)	0.581 ± 0.057	0.727 ± 0.063	0.00000186
Left occipital	(106.08, 149.69, 74.31)	0.204 ± 0.023	0.303 ± 0.078	0.0000457
Right precuneus	(50.92, 147.74, 82.93)	0.358 ± 0.067	0.511 ± 0.051	0.00000164
Left superior temporal gyrus	(141.42, 119.77, 78.50)	0.291 ± 0.049	0.411 ± 0.052	0.00000254
Right parietal operculum	(46.77, 120.15, 93.84)	0.304 ± 0.028	0.422 ± 0.038	0.00000000175
Right superior parietal lobule	(68.65, 127.45, 123.73)	0.438 ± 0.067	0.585 ± 0.059	0.00000545

FA, fractional anisotropy; TBI, traumatic brain injury; MNI, Montreal Neurological Institute.

TABLE 2. MD (MEAN ± STANDARD DEVIATION) FOR MTBI PATIENTS AND CONTROLS (*T*-TEST, 2-TAILED)

Region	*MNI coordinates*	*Subjects*	*Controls*	p-*value*
Right orbitofrontal	(75.76, 54.82, 58.11)	0.628 ± 0.054	0.590 ± 0.028	0.0488
Right anterior limb of internal capsule	(76.45, 81.63, 70.82)	0.592 ± 0.039	0.548 ± 0.058	0.0263
Corpus callosum genu	(88.67, 63.32, 71.88)	0.760 ± 0.087	0.674 ± 0.084	0.0189
Left occipital	(106.08, 149.69, 74.31)	0.713 ± 0.099	0.632 ± 0.093	0.0464
Right precuneus	(50.92, 147.74, 82.93)	0.612 ± 0.054	0.524 ± 0.046	0.000218
Left superior temporal gyrus	(141.42, 119.77, 78.50)	0.672 ± 0.109	0.586 ± 0.018	0.0207
Right parietal operculum	(46.77, 120.15, 93.84)	0.633 ± 0.045	0.548 ± 0.196	0.00000665
Right superior parietal lobule	(68.65, 127.45, 123.73)	0.594 ± 0.061	0.514 ± 0.060	0.00296

MD, mean diffusivity; TBI, traumatic brain injury; MNI, Montreal Neurological Institute.

TBI (Liu et al., 1999; Jones et al., 2000; Takayama et al., 2000; Nakahara et al., 2001; Rugg-Gunn et al., 2001; Arfanakis et al., 2002; Hergan et al., 2002; Huisman et al., 2003; Ptak et al., 2003; Hvismal et al., 2004; Inglese et al., 2005; Nakayama et al., 2006; Tisserand et al., 2006; Kraus et al., 2007; Niogi et al., 2008), three aspects of our study population as well as our approach to data analysis are noteworthy. First, we report findings in a group of cognitively impaired mTBI patients who were neurologically normal at the time of injury. Such late recognition of cognitive impairment is characteristic of mTBI (CDC, 2003).

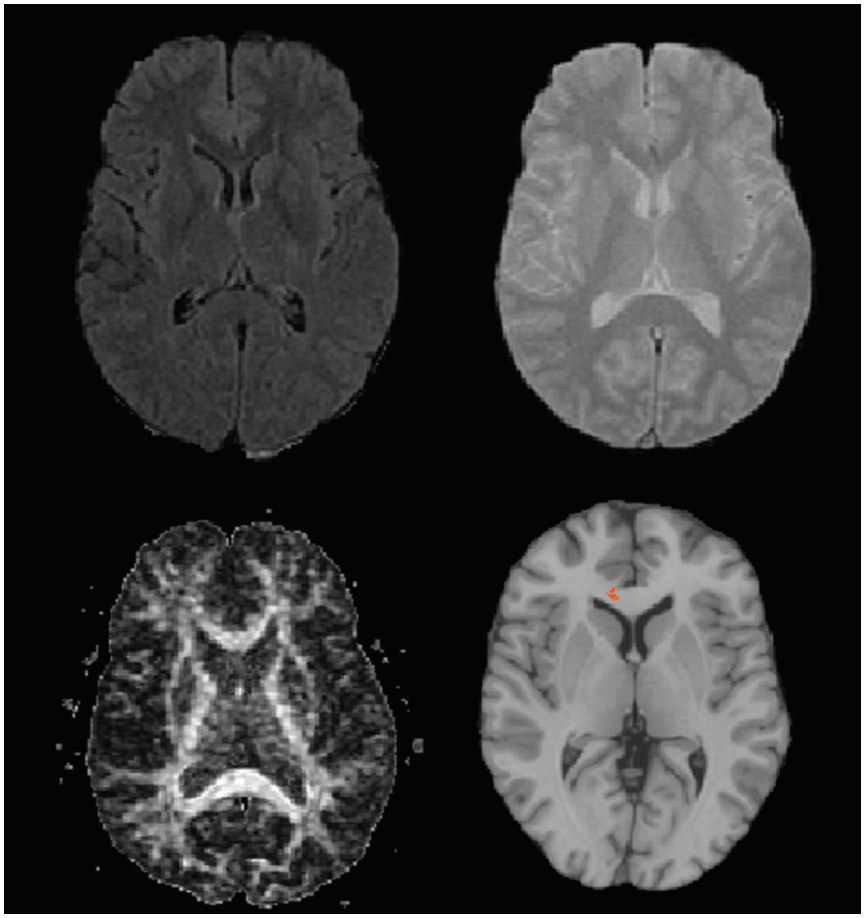

FIG. 3. Voxel-wise analysis of fractional anisotropy (FA) in a single subject. Analysis of FA in a 50-year-old woman following mild traumatic brain injury. Axial noncontrast FLAIR (top left; TR = 11,000 msec, TE = 120 msec, TI = 2800 msec) and GRE (top right; TR = 650 msec, TE = 16 msec, flip angle 18°) images from a single subject at the level of the genu of the corpus callosum (top row) show no abnormality, including no evidence of old hemorrhage. Areas where FA is significantly lower in the single subject are shown as colored regions (lower right) superimposed on an axial Montreal Neurological Institute (MNI) template image. Despite the significantly lower FA found in this subject's genu, no clear abnormality is visible in the FA image (lower left). Lower FA than controls was also found at other locations (not shown). While not as numerous, the lesions found in single subjects co-locate with significantly lower FA found in analysis of the entire patient and control groups.

Second, we have addressed an important and prevalent outcome of mTBI. Cognitive impairment occurs in as many as 30% of patients (Alexander, 1995; Kushner, 1998). While the neurobehavioral symptoms of cognitive impairment may be nonspecific, they lead to substantial morbidity and disability (Kushner, 1998; 2003). Studies of disability and neuropsychological outcomes using DTI have only been reported in severe TBI (Ptak et al., 2003; Huisman et al., 2004; Ewing-Cobbs et al., 2006; Nakayama et al., 2006). Kraus et al. reported a study of chronic mTBI, showing correlation of white matter abnormalities with cognitive impairment in a region of interest (ROI) analysis (Kraus et al., 2007). Our findings are congruent with those of Kraus, but since the voxel-wise analysis surveys the entire brain at high resolution, we are additionally able to depict the distribution of even small brain lesions, showing a pattern of abnormalities in mTBI that is similar to DAI. Even more recently, Niogi et al. reported voxel-wise analysis of DTI in mTBI and showed correlation of white matter abnormalities with a single reaction time measure (Niogi et al., 2008). This study evaluated a range of time after injury and was not restricted to chronic patients; imaging occurred as early as 1 month after injury, well within the timeframe over which recovery from mTBI is still occurring. Thus, we can be more assured that the abnormalities in the present study represent true chronic mTBI pathology.

Third, we have evaluated patients in the chronic phase of the disorder. While both symptoms and brain lesions may manifest at presentation in severe TBI, mTBI generally presents few if any findings at the time of injury (Kushner, 1998). mTBI pathology evolves following the initial trauma, due to a cascade of cellular and systemic responses (Gentry, 1994; McArthur et al., 2004; Nortje and Menon, 2004), leading to delayed evolution of both brain pathology and clinical deficits.

Finally, the voxel-wise approach employed in this study reduces potential biases by standardizing the analysis and improves sensitivity by minimizing partial volume effects. The ROI analysis method that has been used in previous reports of DTI in TBI (Arfanakis et al., 2002; Ptak et al., 2003; Huisman et al., 2004; Lo et al., 2006), has significant limitations including observer bias inherent in ROI placement and partial volume effects when placing white matter ROIs in close proximity to gray matter or CSF. Since FA images have relatively low spatial resolution and low contrast-to-noise, it is difficult to identify anatomic landmarks to guide ROI placement. In this study, since each subject's brain is transformed to a standard brain-space using validated, robust and automated algorithms, we minimize uncertainty inherent in manual placement of ROIs across subjects. Despite the care taken in performing image registration, small registration errors may occur, particularly at the edges of the brain volume. However, there is no reason to expect these artifacts to occur in a systematic manner that selectively affects one group, leading to false positive findings. It is much more likely that such errors would mask real findings. Thus, we feel that our findings represent a conservative measure of the extent of true brain abnormalities.

The distribution of abnormalities found in our subject group is concordant with pathological and imaging studies of diffuse axonal injury (DAI) (McArthur et al., 2004). DAI typically follows severe trauma, with impairment at the time of injury and poor prognosis. The similar distribution of our findings suggests that mTBI represents one end of a DAI spectrum (Povlishock and Jenkins, 1995). This similarity may have great importance for treatment of TBI. Treatment trials in DAI, focusing on cellular injury, including neuroprotective, anti-inflammatory, and receptor blocking or neurotransmitter scavenging agents, have been universally disappointing (Meythaler et al., 2001). This may be because severe injury causes immediate tissue disruption that is not reversible. In mTBI, however, treatment initiated at the time of injury might be able to prevent progression to irreversible brain damage. If DTI abnormalities are also present at the time of injury, mTBI patients at risk for progression to permanent brain damage might be identified before deficits manifest. DTI could then be evaluated as a screening tool to stratify patients as to prognosis and need for treatment as well as provide a criterion for use in future treatment trials in TBI. Even if DTI findings are not confirmed at the time of injury, confirmation of latent findings suggests a progressive injury that may be more amenable to treatment than severe TBI.

Normalization of brain images provides a powerful means for making automated and objective inter-subject and inter-group comparisons, but may introduce error, especially if distortion is present in the original diffusion-weighted images due to eddy current or magnetic susceptibility-related effects. Our images were corrected for the effects of eddy currents and we employed a validated method to correct for distortion prior to image analysis. Additionally, we registered each subject's DTI images to their own T2-weighted FSE images, which were subsequently registered to their high-resolution T1-weighted images and, finally, to a high-resolution T1-weighted template. This approach minimizes the potential for error in inter-modality inter-subject registration and assures the most accurate registration of subjects that is possible. The approach we employed has been compared to several other methods, including AIR, AFNI, SPM (Ardekani et al., 2005), and FSL (unpublished results), and performs equal to or better than all.

A potential problem inherent in a voxel-wise analysis, where each voxel is treated individually, is the likelihood of Type I errors (false positive findings), due to the numerous simultaneous comparisons that are made. Brain volumes the size of the voxels employed in this study, however, are not likely to be functionally independent of each other; we expect that lesions will span many voxels. Nonetheless, we have taken several steps to address and control for this issue. We controlled for Type I errors using the FDR measure (Benjamini and Hochberg, 1995), choosing a statistical threshold to ensure that the percentage of false positives relative to the total number of rejected hypotheses did not exceed 1%. Additionally, the clustering algorithm used in the final stages of the analysis requires statistical significance not just at the voxel level, but also across a cluster of contiguous voxels. Finally, we discarded clusters comprising fewer than 100 voxels. These stringencies make us confident that our conclusions are based on an extremely conservative assessment of the data, with the likelihood that white matter injury is even more widespread in mTBI associated with cognitive impairment than we report here.

Differences in the brain-wide distribution of white matter FA in patients and controls further support the strength of our findings. The histogram analysis is entirely free from the

potential biases introduced by regional analyses (ROI or voxel-wise) as all voxels are considered without regard for location. The main limitation of this approach is its lack of sensitivity; if few voxels differ between the groups, effects might not be detectable. Thus, the fact that we do detect group differences in the FA histogram that are consistent with the voxel-wise and ROI analyses, further supports the validity of our findings.

Notably, even evaluation of single subjects revealed foci of lower FA than controls in every case. This finding was not expected because analysis of such a small patient sample ($n = 1$) should be highly underpowered to detect such effects. Nonetheless, the single subject findings suggest that the magnitude of effect seen using DTI may ultimately be amenable to true clinical application where measurements must be made in single subjects.

Several additional limitations of this study bear mention. The sample size is small and our findings must be confirmed in a larger group. Nonetheless, a conservative approach to data analysis was used and the study was powered to detect the effects reported. The patients studied all met criteria for mTBI and had documented cognitive impairment. However, due to the retrospective nature of the study, patients did not undergo standardized cognitive assessments on a standardized follow-up schedule. Our findings indicate that a prospective trial, in which standardized clinical and cognitive evaluations are administered on a strict timeline, is likely to be informative.

We have shown that DTI can identify abnormalities in patients cognitively impaired following mTBI. While the findings hold promise for identifying mTBI patients who have cognitive impairment, they do not necessarily imply that DTI can be used to identify such patients before the onset of neurobehavioral symptoms. That question is most important as its answer could facilitate early identification of the 15% or more of patients who are at risk for cognitive decline following mTBI (Alexander, 1995; Kushner, 1998). Such early identification could certainly be used to define prognosis, but more importantly might serve as a proxy endpoint in the study of novel treatments with potential for preempting late cognitive disability altogether.

Author Disclosure Statement

No competing financial interests exist.

References

Alexander, M.P. (1995). Mild traumatic brain injury: pathophysiology, natural history, and clinical managment. Neurology 45, 1253–1260.

Ardekani, B.A. (1995). A fully automatic multimodality image registration algorithm. J. Comput. Assist. Tomogr. 19, 615–623.

Ardekani, B.A., Bachman, A.H. et al. (2001). A quantitative comparison of motion detection algorithm of FMRI. Magn Reson. Imaging 19, 959–963.

Ardekani, B.A., Guckemus, S., Bachman, A., Hoptman, M.J., Wojtaszek, M., and Nierenberg, J. (2005). Quantitative comparison of algorithms for inter-subject registration of 3D volumetric brain MRI scans. J. Neurosci. Methods 142, 67–76.

Arfanakis, K., Haughton, V.M, Carew, J.D., Rogers, B.P., Dempsey, R.J., and Meyerand, M.E. (2002). Diffusion tensor MR imaging in diffuse axonal injury. AJNR Am. J. Neuroradiol. 23, 794–802.

Benjamini, Y., and Hochberg, Y. (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Statist. Soc. B 57, 289–300.

CDC (Centers for Disease Control and Prevention). (2003). *Report to Congress on Mild Traumatic Brain Injury in the United States: Steps to Prevent a Serious Public Health Problem.* Centers for Disease Control and Prevention: Atlanta.

Ewing Cobbs, L., K.M. Hasan et al. (2006) Corpus Callosum diffusion anisotrophy correlates with neuropsychological outcomes in twins discordant for traumatic brain injury. AJNR Am J Neuroradiol. 27(4):879–881.

Gamlooa, A.M., JR, G.H. Holland et al. (2006). "American Community Survey: earnings and employment for persons with traumatic brain injury." *Neuro Rehabilitation* 21(4): 327–333.

Gentry, L.R. (1994). "Imaging of closed head injury." Radiology 191(1):1–17.

Gentry, L.R., J.C. Godersky, et al. (1988). "Prospective comparitive study of intermediate-field MR and CT in the evaluation of closed head trauma." *Am J Roentgenol.* 150(3):673–682.

Hergan, K., Schaefer, P.W., Sorensen, A.G., Gonzalez, R.G., and Huisman, T.A. (2002). Diffusion-weighted MRI in diffuse axonal injury of the brain. Eur. Radiol. 12, 2536–2541.

Huisman, T.A., Schwamm, L.H., Schaefer, P.W., Koroshetz, W.J., Shetty-Alva, N., Ozsunar, Y., Wu, O., and Sorensen, A.G. (2004). Diffusion tensor imaging as potential biomarker of white matter injury in diffuse axonal injury. AJNR Am. J. Neuroradiol. 25, 370–376.

Huisman, T.A., Sorensen, A.G., Hergan, K., Gonzalez, R.G., and Schaefer, P.W. (2003). Diffusion-weighted imaging for the evaluation of diffuse axonal injury in closed head injury. J. Comput. Assist. Tomogr. 27, 5–11.

Inglese, M., Makani, S., Johnson, G., Cohen, B.A., Silver, J.A., Gonen, O., and Grossman, R.I. (2005). Diffuse axonal injury in mild traumatic brain injury: a diffusion tensor imaging study. J. Neurosurg. 103, 298–303.

Jones, D.K., Dardis, R., Ervine, M., Horsfield, M.A., Jeffree, M., Simmons, A., Jarosz, J., and Strong, A.J. (2000). Cluster analysis of diffusion tensor magnetic resonance images in human head injury. Neurosurgery 47, 306–313.

Kelly, A.B., Zimmerman, R.D. et al. (1998). Head traumas comparison of MR and CT experience in 100 patients. AJMR Am. J. Neuroradiology. 9, 699–708.

Kraus, M.F., Susmaras, T., Caughlin, B.P., Walker, C.J., Sweeney, J.A., and Little, D.M. (2007). White matter integrity and cognition in chronic traumatic brain injury: a diffusion tensor imaging study. Brain 130, 2508–2519.

Kushner, D. (1998). Mild traumatic brain injury: toward understanding manifestations and treatment. Arch. Intern. Med. 158, 1617–1624.

Lim, K.O., Avdekam, B.A. et al. (2006). Voxelwise correlational analysis of white matter integnity in multiple cognitive domains in shizophrenia. Am. J. Psychiatry 163, 2008–2010.

Liu, A.Y., Maldjian, J.A., Bagley, L.J., Sinson, G.P., and Grossman, R.I. (1999). Traumatic brain injury: diffusion-weighted MR imaging findings. AJNR Am. J. Neuroradiol. 20, 1636–1641.

Lo, C., Lipton, M. et al. (2006). Diffusion Tensor (DTI) Distinguishes Patients with Cognitive Improvement Following Mild Traumatic Brain Injury (TBI). Proceedings of the American Society of Neuroradiology, San Diego, CA.

McArthur, D.L., Chute, D.J., and Villablanca, P. (2004). Moder-

ate and severe traumatic brain injury: epidemiologic, imaging, and neuropathologic perspectives. Brain Pathol. 14, 185–194.

Meythaler, J.M., Peduzzi, J.D., Eleftheriou, E., and Novack, T.A. (2001). Current concepts: diffuse axonal injury-associated traumatic brain injury. Arch. Phys. Med. Rehabil. 82, 1461–1471.

Nakahara, M., Ericson, K., and Bellander, B.M. (2001). Diffusion-weighted MR and apparent diffusion coefficient in the evaluation of severe brain injury. Acta Radiol. 42, 365–369.

Nakayama, N., Okumura, A., Shinoda, J., Yasokawa, Y.T., Miwa, K., Yoshimura, S.I., and Iwama, T. (2006). Evidence for white matter disruption in traumatic brain injury without macroscopic lesions. J. Neurol. Neurosurg. Psychiatry 77, 850–855.

Niogi, S.N., Mukherjee, P., Ghajar, J., Johnson, C., Kolster, R.A., Sarkar, R., Lee, H., Meeker, M., Zimmerman, R.D., Manley, G.T., and McCandliss, B.D. (2008). Extent of microstructural white matter injury in postconcussive syndrome correlates with impaired cognitive reaction time: a 3T diffusion tensor imaging study of mild traumatic brain injury. AJNR Am. J. Neuroradiol. 29, 967–973.

Nolin, P., and Heroux, L. (2006). Relations among sociodemographic, neurologic, clinical, and neuropsychologic variables, and vocational status following mild traumatic brain injury: a follow-up study. J. Head Trauma Rehabil. 21, 514–526.

Nortje, J., and Menon, D.K. (2004). Traumatic brain injury: physiology, mechanisms, and outcome. Curr. Opin. Neurol. 17, 711–718.

Povlishock, J.T., and Jenkins, L.W. (1995). Are the pathobiological changes evoked by traumatic brain injury immediate and irreversible? Brain Pathol. 5, 415–426.

Ptak, T., Sheridan, R.L., Rhea, J.T., Gervasini, A.A., Yun, J.H., Curran, M.A., Borszuk, P., Petrovick, L., and Novelline, R.A. (2003). Cerebral fractional anisotropy score in trauma patients: a new indicator of white matter injury after trauma. AJR Am. J. Roentgenol. 181, 1401–1407.

Rugg-Gunn, F.J., Symms, M.R., Barker, G.J., Greenwood, R., and Duncan, J.S. (2001). Diffusion imaging shows abnormalities after blunt head trauma when conventional magnetic resonance imaging is normal. J. Neurol. Neurosurg. Psychiatry 70, 530–533.

Smith, S.M., Jenkinson, M. et al. (2004). Advances in functional and structural MR image analysis and implementation as FSL. Neuroimage. 23, 5208–5219.

Takayama, H., Kobayashi, M., Sugishita, M., and Mihara, B. (2000). Diffusion-weighted imaging demonstrates transient cytotoxic edema involving the corpus callosum in a patient with diffuse brain injury. Clin. Neurol. Neurosurg. 102, 135–139.

Tisserand, D.J., Stanisz, G., Lobaugh, N., Gibson, E., Li, T., Black, S.E., and Levine, B. (2006). Diffusion tensor imaging for the evaluation of white matter pathology in traumatic brain injury. Brain Cogn. 60, 216–217.

Weight, D.G. (1998). Minor head trauma. Psychiatr. Clin. North Am. 21, 609–624.

Wieshmann, U.C., Symons, M.R. et al. (1999). Blunt-head trauma with widespread water diffusion changes. Lancet 353, 1242–1243.

Address reprint requests to:
Michael L. Lipton, M.D.
Department of Radiology
Montefiore Medical Center
111 East 210th Street
Bronx, NY 10467

E-mail: mlipton@aecom.yu.edu