Diffusion-Tensor Imaging Implicates Prefrontal Axonal Injury in Executive Function Impairment Following Very Mild Traumatic Brain Injury[1]

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Purpose: To determine whether frontal white matter diffusion abnormalities can help predict acute executive function impairment after mild traumatic brain injury (mTBI).

Materials and Methods: This study had institutional review board approval, included written informed consent, and complied with HIPAA. Diffusion-tensor imaging and standardized neuropsychologic assessments were performed in 20 patients with mTBI within 2 weeks of injury and 20 matched control subjects. Fractional anisotropy (FA) and mean diffusivity (MD) images (imaging parameters: 3.0 T, 25 directions, $b = 1000$ sec/mm^2) were compared by using whole-brain voxelwise analysis. Spearman correlation analyses were performed to evaluate associations between diffusion measures and executive function.

Results: Multiple clusters of lower frontal white matter FA, including the dorsolateral prefrontal cortex (DLPFC), were present in patients ($P < .005$), with several clusters also demonstrating higher MD ($P < .005$). Patients performed worse on tests of executive function. Lower DLPFC FA was significantly correlated with worse executive function performance in patients ($P < .05$).

Conclusion: Impaired executive function following mTBI is associated with axonal injury involving the DLPFC.

Supplemental material: *http://radiology.rsnajnls.org/cgi/content/full/2523081584/DC1*

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Radiology

More than 1.1 million cases of mild traumatic brain injury (mTBI) are reported annually in the United States (1). While most patients with mTBI recover, as many as 30% or more will have permanent impairment and 20% of patients with mTBI are unable to return to work (2), costing $80 billion yearly in the United States (1).

mTBI is diagnosed on the basis of history and clinical examination; computed tomographic (CT) and magnetic resonance (MR) imaging results are typically normal (3,4). The Glasgow Coma Scale assesses brain injury severity on the basis of clinical criteria; a Glasgow score of 13–15 is mild. Additional criteria used to diagnose mTBI include loss of consciousness not exceeding 20 minutes, posttraumatic amnesia not exceeding 24 hours, and the absence of abnormalities at conventional imaging (5).

Patients with mTBI exhibit nonspecific symptoms, including headache, dizziness, and behavioral abnormalities (2). Neuropsychologic dysfunction is known to occur after mTBI (6), particularly for executive function and motor control impairment (7,8). Executive function impairment in mTBI likely reflects frontal lobe injury; dorsolateral prefrontal cortex (DLPFC) is essential for normal executive function (9,10) and susceptible to injury in mTBI (11,12).

While the shear forces exerted during mTBI may not be sufficient to cause frank tissue laceration and hemorrhage, two autopsy reports have shown pathologic evidence of injury (13,14), and animal studies have shown ultrastructural axonal abnormalities, such as neurofilament misalignment and impairment of axoplasmic transport after mTBI (15). Animal studies also indicate that injured axons undergo progressive changes with evolution of frank axonal disruption during the weeks following injury (16–18).

While evidence suggests neuropathology that results from mTBI, to our knowledge, no diagnostic test is presently available to confirm the presence of injury in vivo. Diffusion tensor (DT) imaging has recently been used to characterize axonal changes seen in traumatic brain injury (19,20). While DT imaging seems to show brain abnormalities after mTBI (21,22) associated with outcomes (23–25), the ability of DT imaging to identify specific pathologic changes that predict specific functional impairment remains less clear. Previous studies (23–26) have examined the relationship between DT imaging and cognitive function in mTBI but have not directly linked specific acute impairment to evidence of pathologic changes at a specific brain site. Our study was designed to determine whether frontal white matter diffusion abnormalities help predict acute executive function impairment after mTBI.

Advances in Knowledge

- Multifocal frontal white matter axonal injury is detectable in the acute period following mild traumatic brain injury (mTBI).
- Dorsolateral prefrontal cortex (DLPFC) white matter anisotropy correlates with performance on tasks of executive function.
- In patients with mTBI, executive dysfunction correlates with low white matter anisotropy in the DLPFC.

Implications for Patient Care

- Diffusion tensor (DT) imaging provides objective evidence of brain injury related to impairment following mTBI, even in the setting of otherwise normal imaging.
- DT imaging evidence of injury correlates with important functional measures that are known to be adversely affected in mTBI.
- DT imaging shows potential as a diagnostic tool to assess injury and impairment in patients with mTBI.

Materials and Methods

Study Subjects

This study was institutional review board approved and Health Insurance Portability and Accountability Act compliant. Subjects were prospectively enrolled, and written informed consent was obtained. Study procedures were distinct from routine clinical care.

Patients with mTBI.—Twenty consecutive patients with mTBI meeting inclusion and exclusion criteria (Table 1) were recruited from one hospital emergency department between August 2006 and February 2008. Patients presented following mild head injury owing to motor vehicle accidents (n = 18) or falls (n = 2) and were evaluated to rule out brain injury.

All mTBI subjects underwent CT imaging of the brain during their evaluation in the emergency department as part of clinical care.

Control subjects.—Twenty control subjects matched for age and sex were recruited. Control subjects underwent the same MR imaging protocol and cognitive evaluation as did the patient sample group. Similarity of the patient and control groups was confirmed with χ^2 (sex) and Student t (age) tests. Control exclusion criteria included *(a)* history of head injury, *(b)* history of neurologic or

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Abbreviations:
CPT = Continuous Performance Task
DLPFC = dorsolateral prefrontal cortex
DT = diffusion tensor
FA = fractional anisotropy
MD = mean diffusivity
MP-RAGE = magnetization-prepared rapid acquisition gradient echo
mTBI = mild traumatic brain injury

Author contributions:
Guarantor of integrity of entire study, M.L.L.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, M.L.L., E. Gulko, E. Gellella; clinical studies, M.L.L., E. Gulko, M.E.Z., B.W.F., E. Gellella, T.G., K.S.; statistical analysis, M.L.L., E. Gulko, M.K., B.A.A., C.A.B.; and manuscript editing, M.L.L., E. Gulko, M.E.Z., B.W.F., M.K., E. Gellella, T.G., K.S., C.A.B.

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psychiatric disease, and *(c)* history of illicit drug use.

Data Acquisition

Following discharge from the emergency department, patients returned 2–14 days after the injury to complete cognitive testing and brain imaging.

Demographics and behavioral measures.—All study subjects completed the Brain Resource Personal History Questionnaire (Brain Resource Company, Sydney, Australia) to ascertain age, sex, educational attainment, substance use, anxiety, depression, stress, and left or right handedness (26).

Neuropsychologic assessment.—IntegNeuro (Brain Resource Company) was used to quantify executive function. IntegNeuro is a computer-based test with established reliability across all cognitive domains (27,28). Two tests of executive function were selected for use in this study, the Continuous Performance Task (CPT) and the Executive Maze Task (M.E.Z., with 12 years neuropsychologic testing experience).

In the CPT, a series of letters (B, C, D, or G) are presented on a computer touch screen for 200 msec separated by 2.5 seconds. When a letter is presented twice in a row, the participant is asked to press a target button with both index fingers. In total, 125 stimuli are presented, 85 nontarget letters and 20 target letters. The number of errors of omission and commission were recorded as dependent variables.

The Executive Maze Test is a computerized adaptation of the Austin Maze Task (29). Participants are presented with an 8 × 8 matrix of circles on a computer touch screen. The objective is to find a hidden path through the grid by means of trial and error. A tone and a red cross are used to indicate an incorrect move. A different tone and a green checkmark are shown to indicate a correct move. Twenty-four consecutive correct moves are required to transverse the maze. The task ends after the participant completes the maze twice without errors or after 10 minutes, whichever comes first. The number of trials and the time to maze completion were recorded as dependent variables.

Image acquisition.—Imaging was performed (M.L.L., with 18 years MR imaging experience) with a 3.0-T imager (Achieva; Philips Medical Systems, Best, the Netherlands) by using an eight-channel head coil (Sense Head Coil; Philips Medical Systems). T1-weighted whole-head structural imaging was performed by using sagittal three-dimensional magnetization-prepared rapid acquisition gradient echo (MP-RAGE) imaging (repetition time msec/echo time msec, 9.9/4.6; field of view, 240 mm; matrix, 240 × 240; and section thickness, 1 mm). T2-weighted whole-head imaging was performed by using axial two-dimensional turbo spin-echo (4000/100; field of view, 240 mm; matrix, 384 × 512; and section thickness, 4.5 mm) and axial two-dimensional fluid-attenuated inversion recovery turbo spin-echo (1100/120; inversion time, 2800 msec; field of view, 240 mm; matrix, 384 × 512; section thickness, 4.5 mm; and average number of signals acquired, one) imaging. DT imaging was performed by using single-shot echo-planar imaging (3800/88; field of view, 240 mm; matrix, 112 × 89; section thickness, 4.5 mm; independent diffusion sensitizing directions, 32; and b = 1000 sec/mm^2).

Data Analysis

Neuroradiologic image assessment.—Two American Board of Radiology (with a Certificate of Added Qualification) certified neuroradiologists (M.L.L. and K.S., with 12 and 8 years experience, respectively) independently reviewed CT and MR images of all subjects (patients and control subjects) in random sequence during a single session. This review was performed to identify structural abnormalities, including assessment for evidence of hemorrhage. Review took place after completion of all data collection. Reviewers were blinded to all clinical information and group membership (patient or control). Reviewer assessments were concordant in all cases (100%) that no abnormalities were visualized on conventional images. For subject safety, attending neuroradiologists who were American Board of Radiology (M.L.L. and nonauthors, each with a Certificate of Added Qualification)–certified performed a clinical review of each examination contemporaneous with its acquisition but this assessment was not part of the study.

Calculation of diffusion parameter images.—The 33 diffusion-weighted image sets (32 diffusion sensitizing directions and the $b = 0$ sec/mm^2 image) were corrected for head motion and eddy current effects by using an affine registration algorithm (T.G., with 2 years experience in image analysis). Fractional anisotropy (FA) and mean diffusivity (MD) diffusion measures were derived from a DT model at each voxel by using the FMRIB Diffusion Toolbox function (30).

Image analysis.—Quantitative image analysis was performed as follows:

Skull stripping: Nonbrain voxels were removed from the MP-RAGE and turbo spin-echo images by using FMRIB-FSL software (31). Each brain volume was inspected section-by-section, and residual nonbrain voxels were removed manually.

Echo-planar imaging distortion correction: Turbo spin-echo images were acquired with similar section position and orientation as were DT images. Distortion correction was accomplished by using a nonlinear deformation algorithm to

Table 1

Criteria for Study Participants

Inclusion Criteria	Exclusion Criteria
21–50 years of age	Hospitalization owing to the injury
Witnessed closed-head trauma	Abnormal conventional brain imaging
Glasgow Coma Scale score ≥13	History of prior head trauma
Loss of consciousness < 20 minutes	Cognitive impairment before injury
Posttraumatic amnesia < 24 hours	History of neurologic or psychiatric disease
No focal neurologic deficit	History of illicit drug use
English or Spanish proficiency	Litigation related to the injury

match the echo-planar imaging to the turbo spin-echo volumes (32).

Intermediate rigid-body registration: Each subject's turbo spin-echo images were registered to their three-dimensional MP-RAGE images by using the Automated Registration Toolbox three-dimensional (33) rigid-body approach (34).

Registration to standard space: The nonlinear registration module of the Automated Registration Toolbox was used to register each subject's three-dimensional MP-RAGE volume to a standard T1-weighted template (Montreal Neurological Institute atlas) (35).

Transformation of DT images to standard space: By using the Automated Registration Toolbox, distortion correction, intermediate rigid-body registration, and standard space registration were applied to the calculated FA and MD maps by using a single resectioning operation. Final cubic voxel size was 1 mm^3, masked to exclude nonbrain voxels from the analysis.

Segmentation: The fast automated segmentation tool in the FMRIB-FSL software (31) was used to generate a white matter mask for the three-dimensional MP-RAGE template brain images and restrict subsequent statistical analysis of FA to white matter voxels.

Voxelwise statistical analysis: The Automated Registration Toolbox was used to perform a Student *t* test analysis comparing patient versus control FAs at each voxel, covarying for age and sex. Type I errors (false-positive errors) were controlled for by using the false discovery rate measurement in FSL (36). The false discovery rate is the expected proportion of rejected hypotheses that are false-positive results. A false discovery rate of 0.01 corresponded to a *P* value of .01. Thus, we selected a *P* value threshold level of .01 for our analyses to ensure a false discovery rate of less than 0.01 (1%). As an additional safeguard against false-positive results, we only retained clusters that were greater than 100 voxels (100 mm^3) in size.

Statistical images representing significant group differences in FA are displayed as color overlays superimposed on T1-weighted images from the Montreal Neurological Institute template.

Statistical analysis.—Statistical analyses were performed by using software (SAS, version 9.1; SAS Institute, Cary, NC) by a biostatistician (M.K., with 18 years experience).

Bivariate associations of FA and MD with tests of executive function were evaluated by using the Spearman rank correlation coefficient. Multivariate analyses were performed by using linear regression models on the rank-transformed data. The following predictor variables were considered: FA and MD in each region, age, education, sex, depression, stress, anxiety, tobacco use, and alcohol use. The final multivariate model was determined by using a forward selection procedure. Correlations were considered significant for a *P* value of less than .05.

Table 2

Sample Characteristics and Behavioral Measures

Patient Data	Patients ($n = 20$)	Controls ($n = 20$)	*P* Value
Age (y)			
Men	29.9 ± 6.8 (19–40)	30.1 ± 6.5 (21–40)	.94
Women	36.3 ± 8.7 (25–49)	37.6 ± 10.0 (23–52)	.75
Total	33.4 ± 8.3 (19–49)	34.2 ± 9.3 (19–49)	.77
No. of women*	11 (55)	11 (55)	>.99
Education (y)	13.9 ± 2.7	15.5 ± 2.9	.11
Depression	6.0 ± 6.5	1.6 ± 2.2	.02
Stress	8.4 ± 7.9	2.9 ± 3.7	.02
Anxiety	5.8 ± 6.8	0.9 ± 1.3	.01
Left handedness*	4 (20)	0 (0)	.99

Note.—Data are the mean ± standard deviation; numbers in parentheses are the ranges, unless otherwise indicated.

* Data are numbers of patients; numbers in parentheses are percentages.

Table 3

Executive Function Impairment

Function	Patients	Controls	*P* Value
CPT errors of omission	3.21 ± 2.81	1.12 ± 2.39	.03
No. of maze trials	17.25 ± 9.94	9.95 ± 6.24	.008
Maze time (sec)	399 ± 200	278 ± 185	.053

Note.—Data are the mean ± standard deviation.

Results

Eighteen patients sustained their head injury during a motor vehicle accident and two as a result of a fall. The patient and control populations did not differ with respect to age, sex, or education (Table 2). Patients had significantly higher levels of depression ($P = .02$), stress ($P = .02$), and anxiety ($P = .01$) than did control subjects.

Patients performed significantly worse on tests of executive function (Table 3). CPT errors of omission and executive maze number of trials were significantly higher ($P < .05$) in the patient group. Patients tended to take longer to complete the executive maze, although significance was not found ($P = .053$).

Voxelwise analysis of FA images helped detect 15 clusters of lower white matter FA ($P < .005$) in patients compared with control subjects, five of which were located in the frontal lobe (Fig 1 and Fig E1 [*http://radiology.rsnajnls.org/cgi/content/full/2523081584/DC1*]). Mean FA was lower and MD was higher in patients at each of these locations (Table 4).

Scatterplots (Fig 2 and Fig E2 [*http://radiology.rsnajnls.org/cgi/content/*

Figure 1

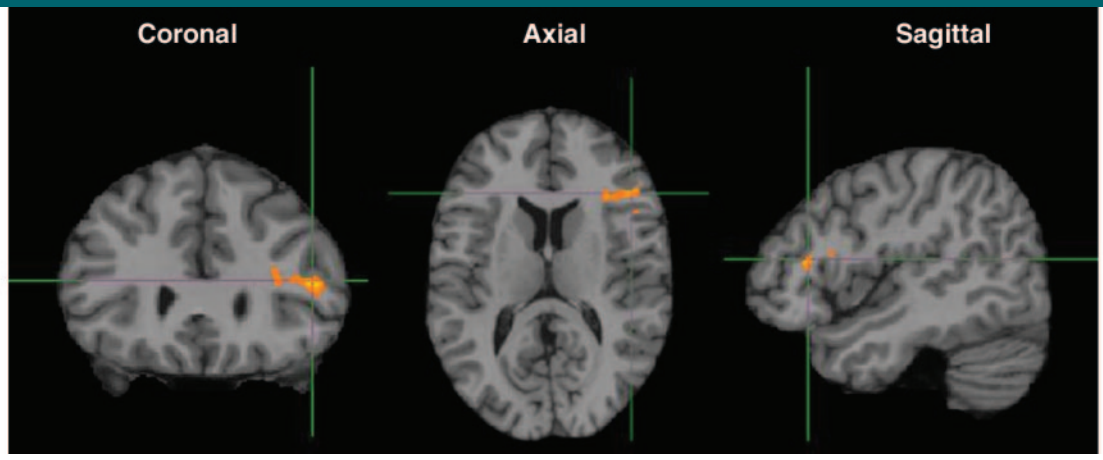

Figure 1: Frontal lobe white matter deficits in mTBI. Color overlays on template brain images show region 1 where frontal white matter FA is lower in patient group ($P < .01$).

full/2523081584/DC1]) demonstrate group differences in FA and executive function between patients and control subjects. The inverse relationship between FA and scores on executive function tasks indicates that lower FA is associated with poorer executive function performance.

Spearman rank correlations demonstrate significant relationships between three of the frontal FA measurements and tasks of executive function (Table 5). The most strongly correlated regions are in the white matter subjacent to the DLPFC on the left. Although not reaching significance, the trend at all locations was for lower FA associated with greater impairment. Results of multivariate analyses indicate that DLPFC FA predicts CPT errors of omission and executive maze number of trials ($P = .02$) as well as Executive Maze time to completion ($P = .05$). Further correlation analyses covarying for age, sex, education, substance use, depression, stress, and anxiety in our multivariate analyses were not found to confound the association between diffusion measures and executive function.

Table 4

Mean Cluster FA and MD for Patients and Controls

Region	Volume (mm^3)	Diffusion Measure	Patients*	Controls*	*P* Value
1	389	FA	0.240 ± 0.047	0.314 ± 0.038	<.0001
		MD	7.69 ± 0.59	7.19 ± 0.50	.007
2	111	FA	0.208 ± 0.062	0.289 ± 0.053	<.0001
		MD	8.12 ± 0.50	7.50 ± 0.64	.0016
3	190	FA	0.307 ± 0.054	0.373 ± 0.036	<.0001
		MD	6.77 ± 0.35	6.38 ± 0.35	.0011
4	120	FA	0.332 ± 0.059	0.417 ± 0.050	<.0001
		MD	7.33 ± 0.49	6.95 ± 0.30	.0046
5	109	FA	0.220 ± 0.065	0.315 ± 0.065	<.0001
		MD	8.53 ± 0.91	8.11 ± 0.96	.16

* Data are the mean ± standard deviation.

Discussion

Detection of ultrastructural damage by using DT imaging is a major advance in diagnostic imaging. Several studies have supported the capability of FA to help identify white matter abnormalities in patients with traumatic brain injury (19,37,38), including mTBI (21–23). As confirmed by our findings, abnormal FA is detected even in the absence of other imaging abnormalities. Conceptually, loss of anisotropy would be expected following injury to axons, and elegant studies of DT imaging in an optic nerve injury model (39) provide a pathologic basis for the inference that lower anisotropy in mTBI reflects axonal injury. However, linking such evidence of structural damage to relevant functional consequences of mTBI remains the essential link in determining the diagnostic utility of DT imaging and its capability to help select and monitor patients for response to conventional and newer treatments. Only by bridging structure and function can DT imaging maximally contribute toward improved outcomes.

Our cohort sustained mild head injury. While all patients had witnessed closed-head trauma, only two cases had loss of consciousness (of only a few minutes each). No patients had any gross brain abnormality, including microhemorrhages. Our cohort was also carefully screened to exclude confounding variables. Our findings underscore the fact that real brain injury occurs after mild trauma and that it is accompanied by brain dysfunction. DT imaging allowed us to demonstrate the brain's pathologic fea-

tures and connect it to functional impairment. It will be important to evaluate these findings longitudinally to determine their utility in forecasting long-term impairment.

Our study demonstrates a structure-function relationship between an important outcome measure and source of morbidity in mTBI and a specific brain region. Executive function underpins many of the common tasks necessary for normal functioning at work and in daily life (40). Executive function, which is largely dependent on the DLPFC (9,10), is commonly impaired after mTBI and is a major contributor to consequent disability (11,41–43). Our findings identify multiple sites of white matter injury after mTBI but most importantly show association of DLPFC injury with impaired executive function.

Figure 2

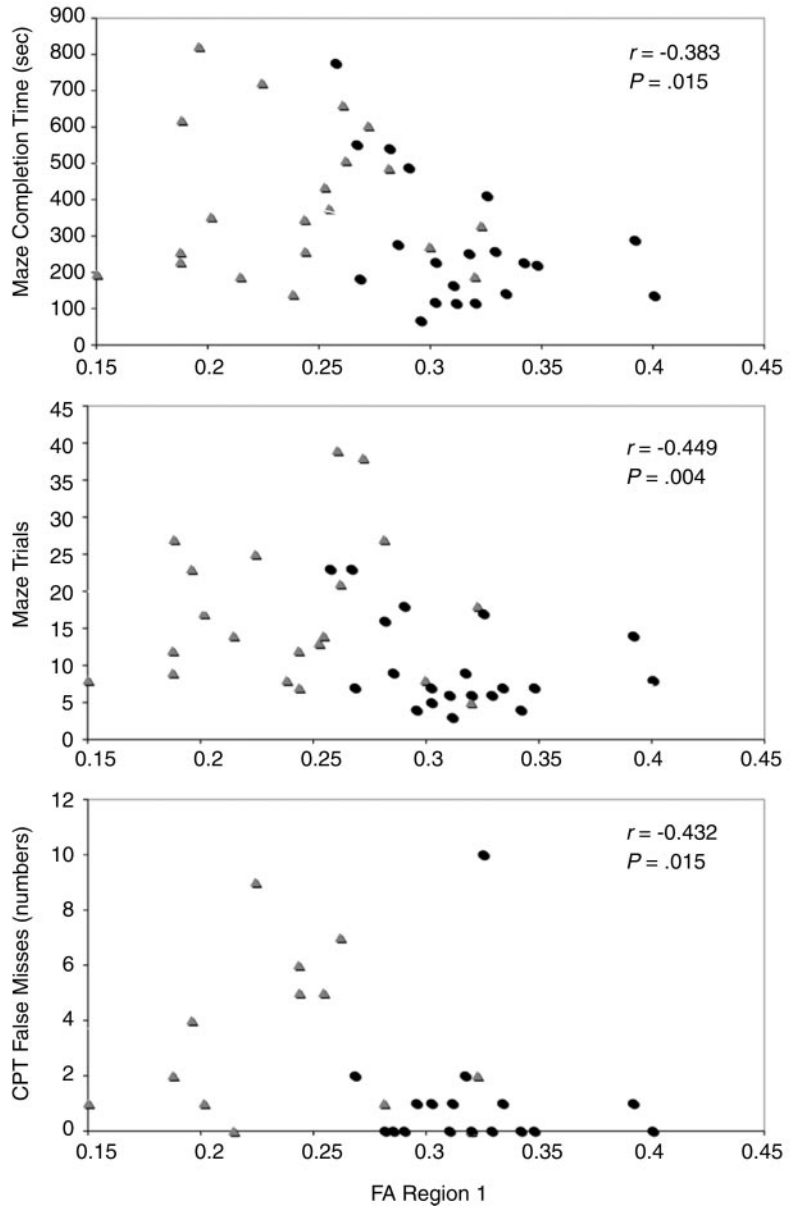

Figure 2: Frontal lobe white matter deficits correlate with executive function impairment. Scatterplots of FA and executive function scores are shown for same frontal lobe location (region 1) as shown in Figure 1. Higher scores on each task indicate decreased performance. Patients (triangles) are compared with control subjects (circles), indicating lower FA and worse executive function performance.

To our knowledge, in the literature, only two reports of patients with mTBI have assessed a quantitative cognitive measure in concert with DT imaging. Kraus et al (24) found an association of lower FA with impairment across many cognitive domains, but in a mixed population of mild, moderate, and severe injury and in the chronic phase. More recently, Niogi et al (25) examined a cohort of patients 1–65 months after injury. Importantly, one-third of the subjects had cerebral hemorrhage, indicating a degree of injury severity. Impaired choice reaction time was associated with the number of abnormal brain regions. Both studies employed region-of-interest analyses to relatively large brain regions. The findings of Kraus et al and Niogi et al implicate a relationship between cognitive performance and FA, but in more severely injured chronic patients with insufficient spatial specificity to identify specific sites of injury that explain performance deficits.

Patients with mTBI are known to have excess stress, anxiety, and depression. Our group also found significant excess morbidity on these behavioral domains in our mTBI group. While multivariate analyses did not support an independent effect of behavioral deficits on the association of DT imaging abnormalities and injury, such an association cannot be entirely ruled out. However, even the presence of such an unrecognized effect would not undermine our inference that frontal white matter injury indexed by using DT imaging is related to functional sequelae of mTBI; behavioral disturbances likely result from brain injury and would thus represent an additional functional consequence of pathologic features of mTBI. Further investigation focused on the behavioral outcomes as primary end points could further clarify their rela-

tionship to DT imaging evidence of pathologic features.

Two major approaches are employed for the interrogation of DT imaging data sets. We used a voxelwise analysis that has been tested and validated in our laboratory (44). The rationale for this choice is to eliminate observer bias and maximize sensitivity to small abnormalities that, given pathologic studies, are known to be the primary lesion of mTBI (15,45). Region-of-interest analyses, in contrast, may be biased during region-of-interest drawing or placement and as a result of partial volume effects.

To minimize the drawbacks of manual region-of-interest placement, voxelwise approaches and many region-of-interest approaches (including that of Kraus et al [24]) employ coregistration of subject images. This approach provides a powerful means for making automated and objective intersubject and intergroup comparisons, but may still introduce error. This is especially true if distortion is present in the original diffusion-weighted images owing 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. To ensure that registration of different image types (DT and MP-RAGE images) and registration of images from individual subjects would be as accurate as possible, we registered each subject's eddy current and motion-corrected DT images to their own T2-weighted turbo spin-echo images, which were subsequently registered to their own high-resolution T1-weighted images and, finally, to a high-resolution T1-weighted template (the Montreal Neurological Institute brain atlas). This approach minimizes the potential for error in intermodality intersubject registration. The approach we employed has been compared with several other methods, including automatic image registration (AIR), analysis of functional neuroimages (AFNI), and statistical parametric mapping (SPM), and performs equal to or better than all (33,34).

Table 5

Correlation of Diffusion Measures with Executive Function

Region	Diffusion Measure	CPT Omissions		Maze Trials		Maze Time	
		r Value	*P* Value	*r* Value	*P* Value	*r* Value	*P* Value
1	FA	−0.432	.015*	−0.449	.004*	−.383	.015*
	MD	0.227	.219	0.229	.156	0.174	.282
2	FA	−0.271	.141	−0.142	.382	−0.69	.672
	MD	0.008	.965	0.00	>.99	0.036	.825
3	FA	−0.236	.201	−0.337	.033*	−0.311	.051
	MD	0.304	.097	0.237	.141	0.223	.167
4	FA	−0.269	.143	−0.215	.183	−0.151	.354
	MD	0.99	.598	0.131	.419	0.116	.477
5	FA	−0.396	.027*	−0.346	.029*	−0.263	.101
	MD	0.012	.950	0.023	.888	0.020	.904

* Significant correlations ($P < .05$).

When performing numerous multiple comparisons in a voxelwise analysis of this magnitude, an important consideration is the occurrence of type I errors (false-positive results). To minimize the likelihood of type I error, we computed the false discovery rate (36). This procedure determines the *P* value at which the number of false-positive results encountered would be less than 1%. Additionally, we required significance at the voxel level as well as between voxels within a cluster, and we only retained clusters of at least 100 voxels in size. These conservative approaches make us confident that our findings represent true abnormalities.

Our study had limitations. We included patients with common forms of mTBI, but other mechanisms, such as a combat-related blast injury might lead to different manifestations of injury. We evaluated patients only during the acute phase after injury. Evidence suggests that the lesions of mTBI develop during the weeks following injury. Thus, our findings may not fully reflect the final extent of injury. Alternatively, just as most patients with mTBI will recover function over time, abnormalities detected by using DT imaging might eventually regress owing to regression of acute abnormalities, such as small amounts of edema or repair of cytoskeletal injury. Longitudinal studies are required to determine the fate of acute DT imaging abnormalities and their relationship to long-term function. Finally, the nature of the voxelwise analysis approach we employed could possibly introduce bias. As described above, we think that we have mitigated this possibility to the greatest extent possible and that our approach is likely to be more sensitive and specific than others.

The imaging diagnosis of brain injury at the time of injury can serve two important purposes. First, it would allow us to document injury with an objective measure and truly ascertain who actually sustains brain injury following trauma. This could allow discrimination of true injury from other disorders presenting with similar nonspecific symptoms as well as from malingering symptoms.

The second potential role for DT imaging is to facilitate early initiation of treatment. Although most patients with mTBI recover function during the months following their injury, as many as 30% retain persistent impairment that leads to substantial disability (2). The deficits of mTBI are often not clinically overt at the time of injury and only attract attention weeks or months later (6). It may be that deficits are simply not noticed initially, are misattributed, or are ignored, but animal models of mTBI suggest that the pathologic features actually evolve over time (46). On the basis of these evolving pathologic features, early intervention may be essential to limit final injury severity. For example, in detecting the pres-

ence of brain injury at the time of injury, DT imaging would allow selection of the subset of patients most likely to benefit from cognitive rehabilitation therapies. Furthermore, DT imaging could be used as a biomarker in clinical trials of novel therapeutics.

In conclusion, we found that lower DLPFC white matter FA in acute mTBI helps predict impaired executive function in these patients. It remains to be determined, given larger longitudinal studies, whether the DT imaging findings at the time of injury are in fact predictive of long-term outcome.

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