Detection of Central White Matter Injury Underlying Vestibulopathy after Mild Traumatic Brain Injury[1]

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Purpose: To determine if central axonal injury underlies vestibulopathy and ocular convergence insufficiency after mild traumatic brain injury (TBI) by using tract-based spatial statistics (TBSS) analysis of diffusion-tensor imaging (DTI).

Materials and Methods: The institutional review board approved this study, and the requirement to obtain informed consent was waived. Diffusion-tensor images were retrospectively reviewed in 30 patients with mild TBI and vestibular symptoms and 25 patients with mild TBI and ocular convergence insufficiency. Control subjects consisted of 39 patients with mild TBI without vestibular abnormalities and 17 patients with mild TBI and normal ocular convergence. Fractional anisotropy (FA) maps were generated as a measure of white matter integrity and were analyzed with TBSS regression analysis by using a general linear model. DTI abnormalities were correlated with symptom severity, neurocognitive test scores, and time to recovery with the Pearson correlation coefficient.

Results: Compared with control subjects, patients with mild TBI and vestibular symptoms had decreased neurocognitive test scores ($P < .05$) and FA values in the cerebellum and fusiform gyri ($P < .05$). Patients with ocular convergence insufficiency had diminished neurocognitive test scores ($P < .05$) and FA values in the right anterior thalamic radiation and right geniculate nucleus optic tracts ($P < .0001$). Cerebellar injury showed an inverse correlation with recovery time ($R = -0.410$, $P = .02$). Anterior thalamic radiation injury showed correlation with decreased processing speed ($R = 0.402$, $P < .05$).

Conclusion: DTI findings in patients with mild TBI and vestibulopathy support the hypothesis that posttraumatic vestibulopathy has a central axonal injury component. Peripheral vestibular structures were not assessed, and a superimposed peripheral contribution may exist. DTI evaluation of central vestibular structures may provide a diagnostic imaging tool in these patients and a quantitative biomarker to aid in prognosis.

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Mild traumatic brain injury (TBI), also referred to as "concussion," affects between 1.8 and 3.8 million individuals in the United States annually (1). Vestibular symptoms are among the most common sequela of mild TBI and among the most hazardous and debilitating, as they put the patient at increased risk for a second injury, impair activities of daily living, and can be difficult to treat (2). Vestibular symptoms are even more common among blast-induced mild TBI and are becoming increasingly more common with the large number of soldiers returning from Iraq and Afghanistan (3).

The mechanism underlying vestibulopathy in mild TBI is poorly understood. Moderate to severe TBI may cause a perilymphatic fistula or posttraumatic Meniere disease, but the relationship between mild trauma and vestibulopathy remains unclear (4). It has been long and widely suspected that vestibular symptoms in mild injury also result from damage to the peripheral vestibular structures rather than central nervous system (5,6). Animal models of acceleration-deceleration injury demonstrate damage to the utricle and saccule (7). Rupture of the otolith structures has been seen in patients with mild TBI (8), and resulting displaced otoconia are the suspected cause of posttraumatic benign paroxysmal positional vertigo (9,10). However, many patients with mild TBI and vestibulopathy also have oculomotor dysfunction, which is indicative of a central injury. Supporting a central etiology of vestibulopathy, postural testing in patients with mild TBI showed that these patients have difficulty in resolving conflicting visual and somatosensory input, indicating a central processing dysfunction (11). Likewise, pathologic findings at vestibular neurectomy have shown shear injury in the brainstem in these patients (12).

We therefore hypothesized that central traumatic axonal injury is a primary feature of the injury pattern underlying posttraumatic vestibulopathy. To test this hypothesis in a noninvasive manner, we used diffusion-tensor imaging (DTI), a neuroimaging technique that is sensitive to subtle changes in white matter fiber tracts and capable of revealing these microstructural axonal injuries that occur with mild TBI (3). Fractional anisotropy (FA) is a DTI metric of the diffusion profile of water, and decreased FA serves as a proxy of axonal injury (13). FA is the most widely accepted DTI metric for evaluating white matter microstructure (13). We used a voxel-wise method in which the FA was measured for each individual image voxel in each patient, enabling evaluation of every region of the brain for a given patient in a single analysis session. Thus, the purpose of this study was to determine if central axonal injury underlies vestibulopathy and ocular convergence insufficiency after mild TBI by using tract-based spatial statistics (TBSS) analysis of DTI.

Advances in Knowledge

- Patients with mild traumatic brain injury (TBI) and vestibular symptoms have decreased fractional anisotropy (FA) in the cerebellum and fusiform gyri ($P < .05$) compared with control subjects, with cerebellar injury showing an inverse correlation with recovery time ($R = -0.410$, $P = .02$).
- Patients with mild TBI and ocular convergence insufficiency have decreased FA in the right anterior thalamic radiation and right geniculate nucleus optic tracts compared with control subjects ($P < .0001$), with anterior thalamic radiation injury showing a correlation with decreased processing speed ($R = 0.402$, $P < .05$).

Implication for Patient Care

- The detection of a central diffuse axonal injury underlying posttraumatic vestibulopathy indicates that diffuse axonal injury is responsible for more postconcussion symptoms than simply the cognitive and executive deficits investigated previously; this has the potential to change the current clinical management of vestibulopathy in mild TBI, which previously lacked both an understanding of the central component of the underlying injury, as well as biomarkers to aid in prognosis.

Materials and Methods

Subjects

Our institutional review board approved this study, and the requirement to obtain informed consent was waived. All studies included were performed as the standard of care, and results were retrospectively reviewed.

We searched our electronic medical records to retrospectively identify magnetic resonance (MR) imaging studies performed with DTI for mild TBI. Radiology reports from March 1, 2006, to March 1, 2013, were searched by using keywords "concussion" and "diffusion-tensor imaging." Inclusion criteria were age 10–50 years, witnessed closed head trauma, no focal neurologic deficit, loss of consciousness for less than 1 minute, posttraumatic amnesia of less than 30 minutes, and English language proficiency. Exclusion criteria were abnormal conventional brain MR images (three patients), lack of DTI (four patients), unavailable neurocognitive symptom score (six patients), history of ocular convergence abnormality (0

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Abbreviations:
DTI = diffusion-tensor imaging
FA = fractional anisotropy
ROI = region of interest
TBI = traumatic brain injury
TBSS = tract-based spatial statistics

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Guarantors of integrity of entire study, L.M.A., S.F.; 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, all authors; clinical studies, all authors; statistical analysis, L.M.A., K.Y.; and manuscript editing, all authors

Conflicts of interest are listed at the end of this article.

patients), or a symptom score of zero (three patients).

Patients were classified as having vestibulopathy if there was any mention in the electronic medical records of any new vestibular symptoms or abnormal vestibular testing at any time point after injury, including dizziness (reported or provocative), subjective balance difficulties or dysequilibrium, vertigo, oscillopsia, gaze instability, saccadic eye movements, slowed or abnormal oculomotor movements, convergence insufficiency, nystagmus, abnormal cerebellar testing, difficulty with eye tracking, or abnormal balance testing. All patients also underwent ocular convergence testing and were classified as having convergence insufficiency if the medical record indicated there was a reduced near point of convergence of more than 6 cm from the bridge of the nose (clinical examination was performed by a clinical neuropsychologist with 13 years of experience in treating concussion patients [M.C.], and chart review was performed by two Certificate of Added Qualification–certified neuroradiologists [L.M.A., S.F.] with 3 years of experience).

The Immediate Post-Concussion Assessment Cognitive Test, a computerized test that measures cognitive function and postconcussion symptoms with use of a seven-point Likert scale over 22 different categories (M.C.), was used for neurocognitive testing.

DTI and Conventional MR Imaging Assessments

Conventional MR imaging and DTI were performed with a 1.5-T unit (Signa; GE Healthcare, Milwaukee, Wis) and a standard head coil. Despite the relatively long length of time over which this study was conducted, all patients and control subjects included in this study underwent an identical imaging protocol with the same magnet system, as follows: sagittal and axial T1-weighted sequences (repetition time, 600 msec; echo time, minimum possible; section thickness, 5 mm; number of signals acquired, one), fast spin-echo axial proton density–weighted sequence (repetition time, 2000–2500 msec; echo time, minimum possible; section thickness, 5 mm; number of signals acquired, one), T2-weighted sequence (repetition time msec/echo time msec, 2000–2500/84–102; section thickness, 5 mm; number of signals acquired, one), fluid-attenuated inversion-recovery sequence (9000–10 000/149; inversion time, 2200 msec), and diffusion-weighted sequence (single-shot echo-planar sequence; repetition time, 10 000 msec; echo time, minimum possible; section thickness, 5 mm; matrix, 128 × 128). Either T2*–weighted gradient-recalled-echo (4400/21, one signal acquired, 90° flip angle, 3-mm-thick sections) or susceptibility-weighted (37/23, one signal acquired, 15° flip angle, 2.4-mm-thick sections) sequences were performed. The field of view ranged from 200 to 240 mm.

DTI was performed with a single-shot echo-planar sequence (4000/80, two signals acquired, 5-mm-thick sections, 128 × 128 matrix, 260-mm field of view). Diffusion gradients were set in 25 noncollinear directions by using two b values (b = 0 and 1000 sec/mm^2).

TBSS Analysis

TBSS from the Functional Software Library package (FMRIB, version 1.1; Oxford Centre for Functional Magnetic Resonance Imaging of the Brain, University of Oxford, Oxford, England) were used to perform analysis of the white matter FA and mean diffusivity with use of a skeleton-based approach to resolve alignment inaccuracies (14).

Image analysis was performed as follows: First, all FA or mean diffusivity images were aligned to the most representative target image. Then, this target image was affine-aligned into a 1 × 1 × 1 mm^3 MNI 152 space (a normalized and averaged brain atlas developed by the Montreal Neurologic Institute). Every image was subsequently transformed to match the MNI 152 space, and a mean FA or mean diffusivity image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts in common among the group. The FA skeleton was then thresholded for an FA of at least 0.2 to suppress areas of extremely low FA or considerable variability.

Every patient's aligned FA or mean diffusivity data were projected onto this skeleton for voxel-based cross-subject statistical analysis. We applied a Monte Carlo permutation test, with regression analysis using a general linear model to investigate the differences in white matter integrity between patients and control subjects, by using threshold-free cluster enhancement with significance at $P < .05$ (5000 permutations), fully corrected for multiple comparisons (family-wise error corrected) (15,16). A nonparametric two-sample t test for independent groups was used to determine whether FA values in patients with and patients without vestibulopathy and patients with and patients without ocular convergence dysfunction were significantly different. White matter fiber tracts corresponding to a particular significant cluster were localized by using the atlases offered by the Functional Software Library (*http://www.fmrib.ox.ac.uk/fsl/data/atlas-descriptions.html#wm*). This processing was performed by two Certificate of Added Qualification–certified neuroradiologists with 3 years of experience (L.M.A., S.F.) and a physician with 3 years of experience in image analysis (K.Y.).

Region of Interest Data Analysis

Region of interest (ROI) analysis was performed to quantify regions of significant difference localized with TBSS for further correlation analysis. ROI analysis was based on the original TBSS mean FA skeleton overlaid with FA differences between patients and control subjects (corrected, voxelwise). Such an approach provided us the ability to determine the size and location of the clusters of significant differences between patients and control subjects. A single ROI mask was created to correspond with the location (in MNI space) and size of the regions of significant difference. FA values of patients and control subjects were then extracted in an automated fashion by using the identical ROI mask along the individual FA skeletons that were aligned onto common space during the TBSS processing and subsequently compared with one-way analysis of variance and the

Table 1

Summary of Demographic and Clinical Characteristics

Characteristic	Vestibulopathy			Convergence		
	With Vestibulopathy ($n = 30$)	Without Vestibulopathy ($n = 39$)	*P* Value*	Convergence Insufficiency ($n = 25$)	Normal Convergence ($n = 17$)	*P* Value*
Average age (y)	17.6 (10–36)	17.5 (14–38)	.98	18.4 (11–36)	17.9 (14–28)	.78
No. of male patients†	24 (80)	23 (59)	.07‡	22 (88)	10 (59)	.06‡
Median time to presentation (d)	19 (2–486)	27 (1–365)	.09	19 (2–486)	22 (1–275)	.88
No. of subjects with previous concussion†	12 (40)	17 (44)	.81‡	12 (48)	10 (59)	.54‡
Average ImPACT total symptom score percentile§	38.6 (1–97)	28.6 (1–75)	.09	38.6 (1–97)	25.8 (1–75)	.12
Average verbal memory score percentile	24.6 (1–92)	39.1 (1–99)	.049	22.9 (1–80)	49.1 (1–92)	.005
Average visual memory score percentile	17.4 (1–65)	36.5 (1–97)	.005	16.0 (1–65)	35.6 (1–90)	.02
Average processing speed percentile	27.5 (1–84)	39.9 (1–95)	.24	27.3 (1–85)	45.5 (1–95)	.046
Average reaction time percentile	32.5 (1–97)	36.3 (1–95)	.62	30.4 (1–91)	49.5 (1–97)	.052
Median time to recovery (wk)	32 (5–252)	29 (1–249)	.76	32 (5–253)	14 (1–189)	.41

Note.—Except where indicated, numbers in parentheses are the range. The presence of vestibulopathy was determined in all 69 patients. Convergence testing results were available for 42 patients.

* *P* values were two tailed and calculated with use of an unpaired *t* test unless otherwise noted.

† Numbers in parentheses are percentages.

‡ Calculated with the Fisher exact test.

§ ImPACT = Immediate Post-Concussion Assessment and Cognitive Test. Scores are percentiles determined by normative data from baseline testing of more than 17 000 athletes as part of their presport participation, with percentile information accounting for both sex and age.

posthoc Tukey test. The Cohen *d* was used to assess effect size. Correlation of FA values extracted from the ROI and the neurocognitive test results and time to recovery was evaluated with Pearson correlation coefficients. Analysis was performed by the two Certificate of Added Qualification–certified neuroradiologists (L.M.A., S.F.).

Additional Statistical Analyses

Statistical analysis of proportions in the demographic data was performed with the Fisher exact test. Means in the demographic data were compared by using an unpaired two-tailed *t* test. $P < .05$ was considered indicative of a statistically significant difference. Analysis was performed by a physician with postgraduate statistics training (L.M.A.).

Results

Subject Characteristics

Sixty-nine patients were included in our study. Of those 69 patients, six patients had vestibulopathy only, two patients had only convergence insufficiency, 23 patients had both vestibulopathy and convergence insufficiency, one patient had vestibulopathy without documentation of ocular convergence testing results, 26 patients had no vestibulopathy without documentation of ocular convergence testing, and 11 patients had neither vestibulopathy nor ocular convergence insufficiency.

Of the 69 patients with mild TBI, 30 had vestibulopathy and 39 did not (control subjects). The median time from injury to clinical presentation was 22 days (range, 1–486 days). The most common mechanism of trauma was sports injury (16 of 30 patients with vestibulopathy, 53%; 27 of 39 control subjects, 69%; $P = .21$), and the second most common mechanism was motor vehicle accident (two of 30 patients with vestibulopathy, 7%; four of 39 control subjects, 10%; $P = .69$). Verbal and visual memory scores at computerized neurocognitive testing were significantly lower in patients with vestibulopathy than in those without vestibulopathy.

Convergence testing results were recorded in 42 of the 69 patients with mild TBI. Twenty-five patients had convergence insufficiency and 17 had normal convergence (control subjects). The median time from injury to clinical presentation for this cohort was 20 days (range, 1–486 days). Processing speed and verbal and visual memory scores at computerized neurocognitive testing were significantly lower in patients with convergence insufficiency than in those with normal convergence.

There were no statistically significant differences in the number of previous concussions in patients with mild TBI with and without vestibulopathy or in patients with mild TBI with and without convergence insufficiency ($P = .81$ and .54, respectively). Demographic and clinical characteristics are summarized in Table 1.

Figure 1

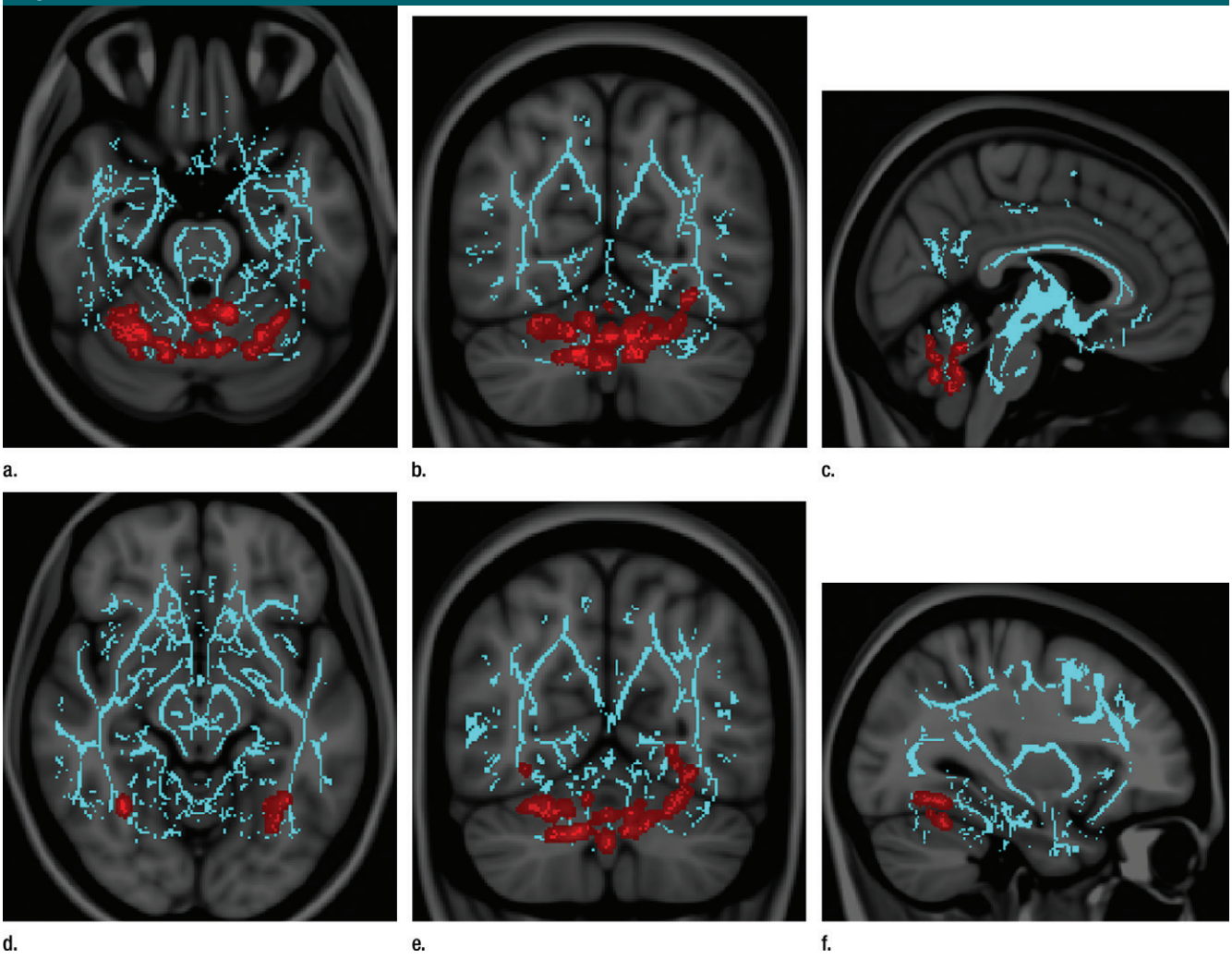


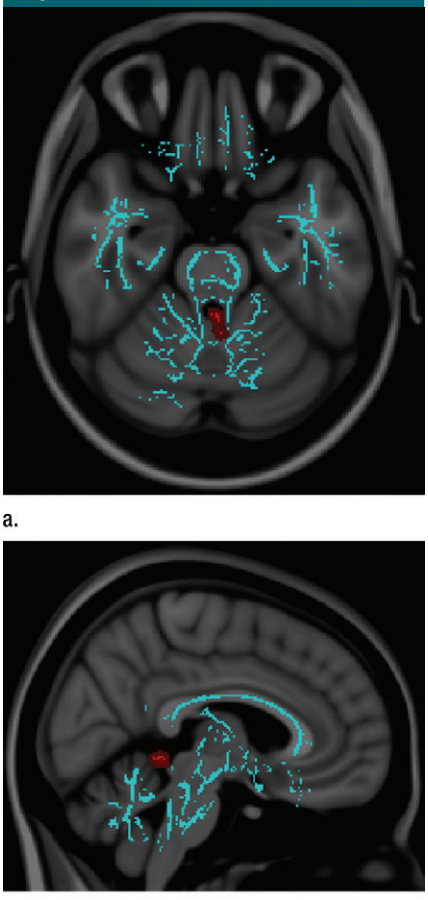
Figure 1: Vestibular disturbances correlate with decreased FA in cerebellar regions responsible for sensorimotor processing and central and/or axial balance as well as fusiform gyrus, which is responsible for visually guided locomotion and stereoscopic vision. Images derived from TBSS results and rendered on T1-weighted images from Montreal Neurologic Institute atlas indicate that significant white matter differences in patients with mild TBI and vestibular symptoms involve **(a–c)** lobule VI and vermian lobules VIIIa, VIIIb, and IX, as shown in axial (**a**), coronal (**b**), and sagittal (**c**) planes, and **(d–f)** fusiform gyri bilaterally, as shown in axial (**d**), coronal (**e**), and sagittal (**f**) planes. Significant voxels ($P < .05$, corrected for multiple comparisons) were thickened by using TBSS fill function into local tracts (red) and overlaid on white matter skeleton (blue).

DTI Assessment with TBSS

Voxel-wise analysis in patients with and patients without vestibulopathy demonstrated that patients with vestibular symptoms had significantly lower FA in the cerebellum and fusiform gyri ($P < .05$). Abnormalities in the cerebellum localized to lobule VI bilaterally as well as to vermian lobules VIIIa, VIIIb, and IX (Fig 1). There were no regions in which the FA was lower in patients without vestibular symptoms than in those with vestibulopathy. Patients with vestibulopathy also had increased mean diffusivity in vermian lobules II and III ($P < .05$) compared with those without vestibular symptoms (Fig 2). There were no regions in which the mean diffusivity was higher in patients without vestibular symptoms than in those with vestibulopathy.

Voxel-wise analysis in patients with and patients without convergence insufficiency revealed that patients with convergence difficulties had significantly lower FA values in the right anterior thalamic radiation and optic radiations of the right lateral geniculate nucleus ($P < .0001$) (Fig 3). There were no regions in which the FA was lower in patients with normal convergence than in those with convergence insufficiency. There

Figure 2

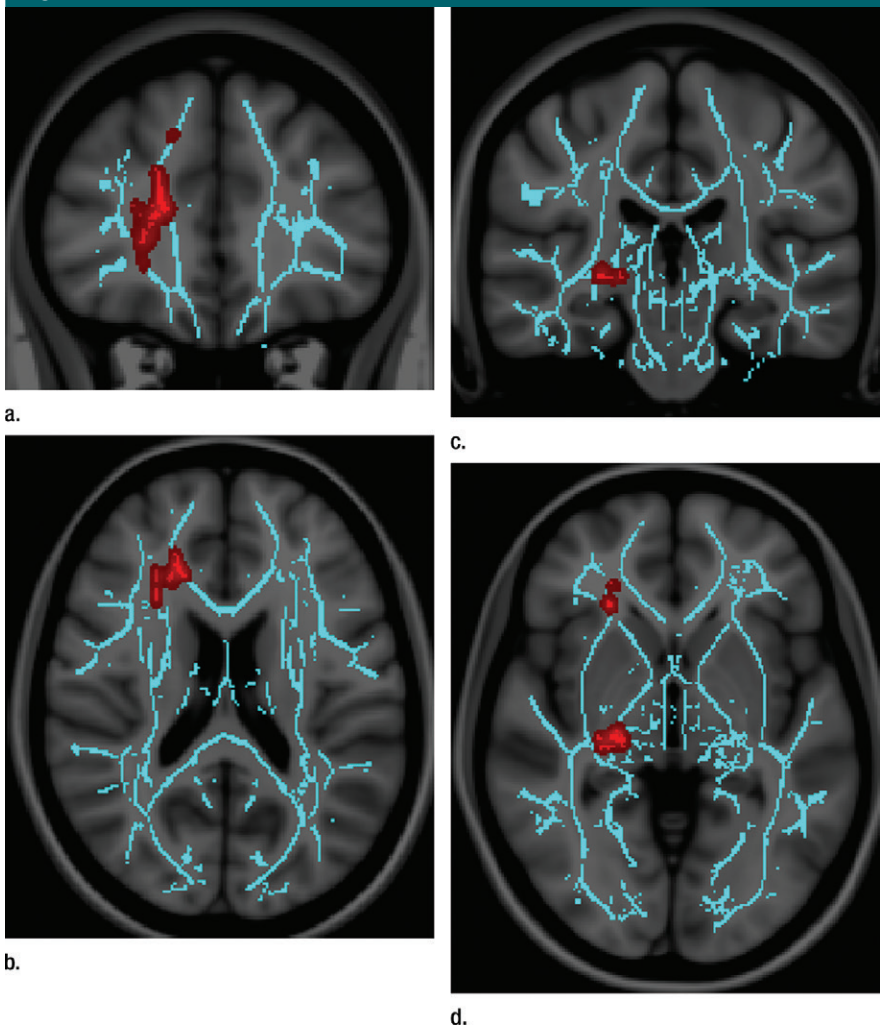


a.

b.

Figure 2: Vestibular disturbances correlate with increased mean diffusivity in vermian lobules of spinocerebellum, which processes proprioception input from spinal cord dorsal columns to anticipate future positioning during the course of a movement. Images derived from TBSS results and rendered on T1-weighted images from Montreal Neurologic Institute atlas indicate that significant white matter differences in patients with mild TBI and vestibular symptoms involve vermian lobules II and III, as shown in **(a)** axial and **(b)** sagittal planes. Significant voxels ($P < .05$, corrected for multiple comparisons) were thickened by using TBSS fill function into local tracts (red) and overlaid on white matter skeleton (blue).

Figure 3



a.

c.

b.

d.

Figure 3: Convergence insufficiency correlates with increased FA in right anterior thalamic radiation, which is central to processing speed, and right geniculate nucleus optic radiations, the major relay station for the accommodation circuit central to oculomotor convergence. Asymmetric involvement of the right is not unexpected, as the corresponding left visual field is dominant for spatial processing as compared with the right visual field, which is dominant for nonspatial and/or temporal processing. Images derived from TBSS results and rendered on T1-weighted images from Montreal Neurologic Institute atlas show that significant white matter differences in patients with mild TBI and convergence insufficiency involve right anterior thalamic radiation, as shown in **(a)** coronal and **(b)** axial planes, and right geniculate nucleus optic radiations; as shown in **(c)** coronal and **(d)** axial planes. Significant voxels ($P < .05$, corrected for multiple comparisons) were thickened by using TBSS fill function into local tracts (red) and overlaid on white matter skeleton (blue).

were no regions in which there was a significant difference in mean diffusivity between patients with and patients without ocular convergence insufficiency.

DTI Assessment with ROI Analysis

In patients with vestibulopathy, FA values in the regions of the cerebellum identified with TBSS showed an inverse correlation with time to recovery ($R = -0.410$, $P = .02$). In patients without vestibulopathy, the correlation with time to recovery was direct ($R = 0.377$, $P = .04$).

In patients with convergence insufficiency, FA values in the anterior thalamic radiation correlated with processing speed ($R = 0.402$, $P = .046$) and trended toward correlation with visual memory scores ($R = 0.350$, $P = .09$). FA values in the lateral geniculate optic radiations trended toward correlation with visual memory score and processing speed ($R = 0.301$, $P = .14$ and $R = 0.370$, $P = .07$, respectively).

Table 2

Comparison of FA in ROIs for Patients according to Presence of Vestibulopathy and Convergence Insufficiency

ROI Location	Patients with Vestibulopathy*	Patients without Vestibulopathy*	Patients with Convergence Insufficiency*	Patients with Normal Convergence*	*P* Value†
Cerebellum	0.239 (0.193, 0.286)	0.260 (0.170, 0.349)	…	…	.03 (−0.59)
Fusiform gyri	0.300 (0.247, 0.353)	0.327 (0.219, 0.434)	…	…	.02 (−0.063)
Anterior thalamic radiation	…	…	0.389 (0.339, 0.438)	0.427 (0.363, 0.491)	.0001 (−1.32)
Right geniculate nucleus optic tracts	…	…	0.544 (0.494, 0.594)	0.581 (0.521, 0.641)	.0001 (−1.34)

* Data are average FA values. Numbers in parentheses are 95% confidence intervals.

† *P* values are two tailed and were calculated with an unpaired *t* test. Numbers in parentheses are the Cohen *d* value.

Results of ROI analysis are summarized in Tables 2 and 3.

Table 3

Correlation of FA with Clinical Findings for ROIs in Patients with Mild TBI and Vestibulopathy and Patients with Mild TBI and Convergence Insufficiency

Parameter	Cerebellum	Fusiform Gyri	Anterior Thalamic Radiation	Right Geniculate Nucleus Optic Tracts
Correlation with symptom severity score	−0.034 (.84)	0.228 (.23)	0.100 (.63)	0.128 (.54)
Correlation with verbal memory score	−0.052 (.78)	−0.064 (.74)	−0.070 (.74)	0.171 (.41)
Correlation with visual memory score	−0.215 (.25)	−0.182 (.34)	0.350 (.09)	0.301 (.14)
Correlation with processing speed score	−0.178 (.35)	−0.292 (.12)	0.404 (.046)	0.370 (.07)
Correlation with reaction time score	−0.036 (.85)	−0.070 (.71)	0.159 (.45)	0.279 (.18)
Correlation with time to recovery	−0.410 (.02)	−0.161 (.40)	0.100 (.63)	0.167 (.42)

Note.—Data are average FAs. Numbers in parentheses are two-tailed *P* values for the Pearson correlation coefficient. Correlation was performed with the Pearson correlation coefficient.

Discussion

Using voxel-based analysis of DTI, we found a central injury pattern underlying posttraumatic vestibulopathy and convergence insufficiency. A substantial number of abnormalities were found in brain regions not previously suspected to be involved in posttraumatic vestibulopathy—specifically, multiple lobules of the cerebellum, as well as fusiform gyri. A central injury pattern was also seen underlying oculomotor dysfunction, with abnormalities in the right lateral geniculate nucleus and anterior thalamic radiations. These regions of abnormality were not only previously unknown but were also correlated with time to recovery, as well as neurocognitive test performance.

Previously, only clinical findings have been correlated with a prolonged return to baseline (17,18), and no specific brain region has been yet implicated in the prolonged recovery time (13). However, in patients with vestibular symptoms, diffusion-tensor abnormalities in the cerebellum correlate with time to recovery, corresponding with clinical observations, as persistent vestibular symptoms can be one of the most important factors impairing return to baseline functioning (4).

Cerebellar injury underlying vestibulopathy localized to lobules II, III, VI, VIII, and IX—which are vital to movement and balance (19). Vermian lobules integrate input from the ascending spinal pathways into balance and movement of the axial skeleton (20). Although cerebellar abnormalities are seen in military blast injuries, it is not a common injury in civilian concussion (21). Our findings may indicate that patients with vestibulopathy experience a mechanism of injury more similar to blast-type injuries than those without vestibular symptoms. The fusiform gyri are also central in movement, visually guided locomotion, stereoscopic vision, and landmark recognition during navigation (22,23).

Oculomotor dysfunction was also known to be present clinically in approximately 90% of patients with mild TBI (24) and is used robustly as a screening tool by the military to assess for mild TBI in combat injuries (25). However, the injury underlying this finding previously had not been elucidated. The optic radiations of the lateral geniculate nucleus are the major relay station for the accommodation neural circuit that controls convergence (26). Correlation with only the right optic radiations corresponds well to known asymmetries in perceptual processing; the left visual field is dominant for spatial information, which is the visual field analyzed by the right lateral geniculate nucleus (27). The anterior thalamic radiation is the principal tract responsible for processing speed (28–30). Notably, tests of processing speed often use oculomotor paradigms (31).

Recent research has shown the effectiveness of both vestibular and vision

therapies in treating patients with mild TBI (32,33). The findings of our study further validate this approach and suggest a synergistic role for DTI and neurocognitive testing in concussion, with DTI able to help confirm a white matter injury suggested with neurocognitive testing. Neurocognitive testing and DTI may together help determine clinical trajectories amenable to treatment and rehabilitation.

The limitations of this study include its retrospective nature and moderate sample size. As such, an attempt should be made to confirm these findings on a prospectively followed up larger cohort. Lack of baseline neurocognitive testing or imaging means that it cannot be excluded that differences in test performance or imaging findings were not the result of uncharacterized baseline differences between the two groups. In addition, many patients with mild TBI do not seek medical attention and the majority do not undergo imaging. Therefore, there is a possibility of selection bias toward more seriously injured patients, who both seek medical attention and have clinical findings significant enough to warrant imaging.

Detection of a central injury underlying symptoms previously suspected to be peripheral indicates that the diffuse axonal injury now detected in mild TBI is responsible for more postconcussion symptoms than simply the cognitive and executive function investigated previously (9). The white matter injury patterns associated with vestibulopathy demonstrate regions of central vestibular dysfunction that were previously not appreciated and allow quantitative measurements to help determine prognosis. This has the potential to change the current clinical management of vestibulopathy in mild TBI, which previously lacked both an understanding of the central component of the underlying injury, as well as biomarkers to aid in prognosis (5,13).

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