Radiology

Combat-related Mild Traumatic Brain Injury: Association between Baseline Diffusion-Tensor Imaging Findings and Long-term Outcomes[1]

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Purpose: To determine whether functional outcomes of veterans who sustained combat-related mild traumatic brain injury (TBI) are associated with scalar metrics derived from diffusion-tensor (DT) imaging at their initial postdeployment evaluation.

Materials and Methods: This HIPAA-compliant retrospective study was approved by the institutional review board, and the requirement to obtain informed consent was waived. From 2010 to 2013, initial postdeployment evaluation, including clinical assessment and brain magnetic resonance (MR) examination with DT imaging, was performed in combat veterans who sustained mild TBI while deployed. Outcomes from chart review encompassed initial postdeployment clinical assessment as well as later functional status, including evaluation of occupational status and health care utilization. Scalar diffusion metrics from the initial postdeployment evaluation were compared with outcomes by using multivariate analysis. Veterans who did and did not return to work were also compared for differences in clinical variables by using *t* and χ^2 tests.

Results: Postdeployment evaluation was performed a mean of 3.8 years after injury (range, 0.5–9 years; standard deviation, 2.5 years). After a mean follow-up of 1.4 years (range, 0.5–2.5 years; standard deviation, 0.8 year), 34 of 57 veterans (60%) had returned to work. Return to work was associated with diffusion metrics in multiple regions of white matter, particularly in the left internal capsule and the left frontal lobe ($P = .02–.05$). Overall, veterans had a mean of 46 health care visits per year during the follow-up period (range, 3–196 visits per year; standard deviation, 41 visits per year). Cumulative health care visits over time were inversely correlated with diffusion anisotropy of the splenium of the corpus callosum and adjacent parietal white matter ($P < .05$). Clinical measures obtained during initial postdeployment evaluation were not predictive of later functional status ($P = .12–.8$).

Conclusion: Differences in white matter microstructure may partially account for the variance in functional outcomes among veterans who sustained combat-related mild TBI.

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Mild traumatic brain injury (TBI) is a public health problem of increasingly recognized importance, particularly among current military veterans. As defined by the Department of Defense (1), mild TBI in veterans refers to a head injury with temporary mental alteration and/or loss of consciousness, with normal findings at conventional neurologic imaging. During the past 2 decades there has been a dramatic increase in the incidence of combat-related mild TBI among U.S. veterans of military operations in Iraq and Afghanistan, the prevalence of which is now reported to be as high as 20% (2). Mild TBI in Operation Iraqi Freedom and Operation Enduring Freedom veterans is primarily caused by blast injuries induced by improvised explosive devices, which are frequently used in modern combat (3). Consequently, mild TBI has become known as the "signature injury" of post-9/11 warfare. Although resolution of posttraumatic symptoms occurs within 3 months in most cases, as many as 25% of individuals with mild TBI will experience chronic physical, cognitive, and affective symptoms (4,5). Furthermore, veterans who have sustained mild TBI are at increased risk of comorbid psychiatric disorders (6), occupational impairment (7), and high levels of health care resource utilization (8,9).

The clinical evaluation and treatment of veterans with combat-related mild TBI remains challenging owing to difficulties in establishing the diagnosis, predicting outcomes, and separating the effects of mild TBI from frequently comorbid psychiatric conditions such as posttraumatic stress disorder (PTSD). Therefore, reliable biomarkers of mild TBI have been sought to better understand the pathophysiology of mild TBI and improve diagnostic accuracy and outcome prediction.

Extensive research conducted during the past decade has demonstrated the potential of diffusion-based magnetic resonance (MR) imaging techniques to detect previously occult abnormalities related to mild TBI (10). The most widely used technique has been diffusion-tensor (DT) imaging, which uses measurements of water diffusion in the brain to infer details of microstructural organization—particularly in white matter. Multiple previous studies have demonstrated alterations of diffusion metrics in groups of veterans who have sustained mild TBI compared with control subjects (11,12). On the basis of work in animal models of TBI, these alterations are hypothesized to represent traumatic white matter injury, predominantly involving axonal damage (13).

Several recent studies have found DT imaging metrics to show correlation with neurocognitive function and short-term functional outcomes in TBI (10,14–16). It is not clear, however, whether DT imaging can help predict longer term outcomes. We therefore set out to determine whether important functional outcomes of combat veterans with a clinical diagnosis of mild TBI are predicted with DT imaging measurements obtained at initial postdeployment evaluation.

Advances in Knowledge

- At their initial postdeployment evaluation, veterans who sustained mild traumatic brain injury (TBI) had elevated Neurobehavioral Symptom Inventory (NSI) scores (mean total score, 39.5); NSI scores showed an inverse correlation with diffusion-tensor (DT) imaging metrics obtained at this time, including fractional anisotropy (FA) within the white matter of the left and right frontal lobes and within the genu of the corpus callosum (P = .016–.05).
- After their initial postdeployment evaluation, 34 of the 57 veterans who sustained mild TBI during combat (60%) returned to work (mean follow-up, 1.4 years); veterans who did not return to work displayed significantly lower FA (P = .02) and significantly higher mean diffusivity (P = .005) within the posterior limb of the left internal capsule compared with those who returned to work.
- After their initial postdeployment evaluation, veterans who sustained mild TBI visited health care providers frequently (mean, 46 visits per year of follow-up); health care utilization showed an inverse correlation with initial postdeployment white matter FA fiber integral within the splenium of the corpus callosum, as well as within multiple adjacent regions (P = .026–.05).

Implication for Patient Care

- This study suggests that DT imaging may be able to help predict functional postdeployment outcomes of veterans who sustained mild TBI during combat.

Materials and Methods

This Health Insurance Portability and Accountability Act–compliant retrospective study was approved by the institutional review board of the home institution. The requirement to obtain informed consent was waived. All MR images included in this study were obtained according to the standard of care.

Published online before print
10.1148/radiol.2016151013 **Content code:** NR

Radiology 2016; 000:1–8

Abbreviations:
DT = diffusion tensor
FA = fractional anisotropy
FAFI = FA fiber integral
NSI = Neurobehavioral Symptom Inventory
PTSD = posttraumatic stress disorder
TBI = traumatic brain injury
TBSS = tract-based spatial statistics

Author contributions:
Guarantors of integrity of entire study, J.B.W., K.M.R., P.G.N.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; manuscript final version approval, all authors; agrees to ensure any questions related to the work are appropriately resolved, all authors; literature research, J.B.W., E.W., P.G.N.; clinical studies, E.W., K.M.R., P.G.N.; statistical analysis, J.B.W., P.G.N.; and manuscript editing, all authors

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

Figure 1

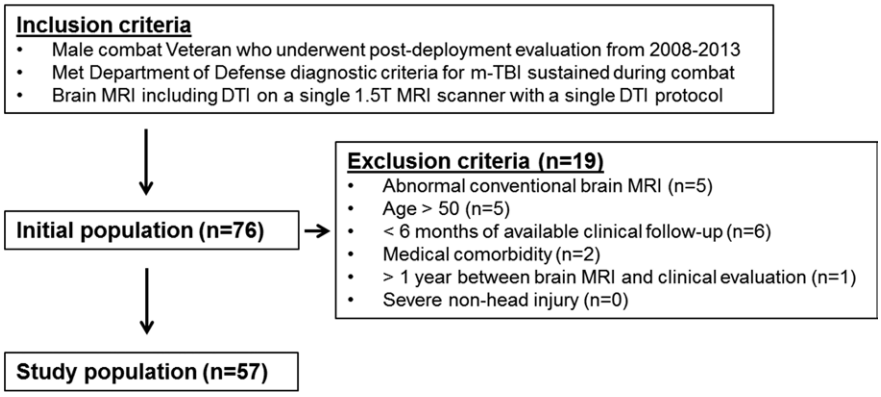

Figure 1: Overview of study population, inclusion criteria, and exclusion criteria. *m-TBI* = mild TBI.

Study Population

All male combat veterans with mild TBI who had undergone brain MR imaging between January 1, 2008, and September 30, 2013, were retrospectively identified within a large Veteran's Administration hospital system. Veterans were routinely referred for brain MR imaging and evaluation by the multidisciplinary Polytrauma Program if they were considered at risk for TBI during postdeployment screening (9). In accordance with Veteran's Administration clinical practice guidelines, the presence or absence of mild TBI was subsequently established at comprehensive evaluation by a physical medicine and rehabilitation physician with particular expertise in the diagnosis and management of combat-related TBI with use of a structured clinical interview. Diagnostic criteria for mild TBI include the combination of an injury to the head and any of the following: transient confusion, disorientation, impaired consciousness, memory dysfunction immediately before or after the time of injury, or loss of consciousness lasting less than 30 minutes (1).

The inclusion and exclusion criteria for this study are outlined in Figure 1. Exclusion criteria included abnormal findings at conventional brain MR imaging, less than 6 months of available follow-up data, age greater than 50 years, any major medical comorbidity at the time of brain MR imaging (eg, human immunodeficiency virus, cardiovascular disease), more than 1 year between clinical evaluation and brain MR imaging, and severe nonhead injury (eg, amputation).

Clinical Data, Injury Characteristics, and Symptoms

Chart review was used to assess demographic, military, clinical, and longitudinal variables for each subject on the basis of documentation from initial postdeployment clinical evaluation, which occurred after each subject's final deployment and within 1 year of the accompanying brain MR imaging. One radiology resident (J.B.W., with 3 years of experience in radiology) manually collected data from the electronic medical record. Demographic variables included age and education level. Self-reported military variables were derived from the most severe head injury experienced by that subject while in combat and included date of injury, mechanism of injury (blast injury vs nonblast injury), and whether loss of consciousness had occurred. In addition, in cases of blast injury, the distance from the blast was estimated by each subject for the closest blast event. For this study, we considered any blast injury of an estimated distance of 30 feet or less to be a "close blast" injury. Clinical variables included medical history, substance use history, psychiatric diagnoses, and neurobehavioral symptom severity. Psychiatric diagnoses included PTSD and major depressive disorder and were made on the basis of clinical interview by a psychiatrist. Neurobehavioral symptom severity was based on the Neurobehavioral Symptom Inventory (NSI), a standardized 22-item symptom-based questionnaire composed of affective, vestibular, cognitive, and somatic symptom clusters (17). NSI scores were compared with a previously published normative reference (18). Within the subgroup of subjects with PTSD, an additional assessment of PTSD symptom severity was made on the basis of the PTSD Checklist–Military Version (19).

Longitudinal variables consisted of postdeployment occupational status at the end of the follow-up period and the number of postdeployment health care visits over time. These variables were assessed on the basis of chart records from all medical and psychiatric visits between the initial postdeployment evaluation and a predefined end point (March 1, 2014). Veterans documented as working full or part time, those actively enrolled in an educational program, and those actively involved in the military at the end of the follow-up period were considered to have returned to work. The number of health care visits over time was calculated by dividing the total number of documented outpatient and inpatient medical and psychiatric visits by the length of follow-up (measured in years) for each subject.

Brain MR Imaging

All veterans in this study underwent brain MR imaging with a 1.5-T unit (Siemens Espree; Siemens, Erlangen, Germany), which included a conventional clinical protocol in addition to a single 30-direction DT sequence with two b values (b = 0 and 1000 sec/mm^2) and the following imaging parameters: repetition time, 5400 msec; echo time, 108 msec; 240-mm field of view; 5-mm-thick sections, and 128 × 128 matrix. Conventional MR imaging sequences included axial high-spatial-resolution T1-weighted, axial fast spin-echo T2-weighted, axial fluid-attenuated inversion recovery, and axial susceptibility-weighted sequences. All MR images received clinical interpretation by a board-certified neuroradiologist.

Table 1

Summary of Demographic, Injury, and Clinical Characteristics

Parameter	Value
Demographic characteristics	
Mean age (y)*	30.5 (22–46)
Some college education or higher	25 (44)
Injury characteristics	
Time from injury (y)*	3.8 (1–9)
Blast mechanism	48 (84)
Close blast (<30 ft)	35 (61)
Loss of consciousness	40 (70)
Comorbid disorders	
PTSD	45 (79)
Depression	19 (33)
Substance use disorder	23 (40)

Note.—Except where indicated, data are numbers of subjects ($n = 57$), with percentages in parentheses.

* Numbers in parentheses are the range.

Table 2

Lack of Association between Clinical Variables and Return to Work

Parameter	Veterans Who Returned to Work	Veterans Who Did Not Return to Work	*P* Value
Mean age (y)	29.8	31.6	.32
Mean time since injury (y)	3.4	4.3	.21
Some college education or higher (%)	44 (15/34)	43 (10/23)	.97
PTSD (%)	76 (26/34)	83 (19/23)	.8
Depression (%)	24 (8/34)	48 (11/23)	.12
Substance use disorder (%)	38 (13/34)	43 (10/23)	.76
Close blast (%)	71 (24/34)	48 (11/23)	.28
Loss of consciousness (%)	68 (23/34)	48 (11/23)	.34
Mean NSI	38.9	40.4	.74

Note.—Numbers in parentheses are raw data.

DT Image Postprocessing

All processing of DT imaging data was performed offline on a single workstation by using the freely available software package tract-based spatial statistics (TBSS) (20), part of the Functional MR Imaging of the Brain software library (21). Data analysis was performed by J.B.W. and P.G.N. (a board-certified neuroradiologist with 9 years of neuroradiology experience). Preparation of DT images for statistical analysis was performed according to the standard TBSS pipeline and included correction of eddy currents, brain extraction, and derivation of subject-specific maps of scalar diffusion metrics by fitting a tensor model to the diffusion data. Scalar diffusion metrics included fractional anisotropy (FA), mean diffusivity, axial diffusivity, and radial diffusivity. FA images were then prepared for statistical analysis by aligning each subject's FA data to a common space by using the nonlinear registration tool *FNIRT*, part of TBSS. A mean FA image was then created, followed by derivation of the mean FA skeleton, representing centers of all tracts common to the group. Each subject's FA map was included in the generation of the mean FA skeleton. Subject-specific maps of the additional diffusion metrics were subsequently prepared by applying the same registration transformation derived in the FA processing steps to each parameter map for each subject. Finally, each subject's aligned data for each scalar metric were projected onto the mean FA skeleton. Subject-specific scalar metric skeleton maps were then used for voxel-wise cross-subject statistics.

In addition to the traditional diffusion metrics, we performed voxel-wise calculation of a FA fiber integral (FAFI). The FAFI value of a voxel is dependent not only on the FA of that voxel but also on FA values elsewhere along white matter tracts that pass through that voxel (22). This method increases the spatial coherence of tract-specific white matter changes, which increases the sensitivity of voxel-wise analysis for tract-specific abnormalities. These features may confer greater overall sensitivity for the detection of diffusion changes, which are spatially heterogeneous and of greater functional importance.

The FAFI was calculated from the FA and principal diffusion direction maps, which are used to perform deterministic tractography from each of eight subseeds within each white matter voxel by using in-house software written in MATLAB (Mathworks, Natick, Mass). FA is then integrated along the extent of each of the resultant tracts and the total FA sum is deposited into the starting voxel, representing the FAFI value. To prepare for statistical analysis, each subject's FAFI map was first aligned into a common space by using the same nonlinear registration process as used for the FA data and then projected onto the mean FA skeleton. Subject-specific FAFI skeleton maps were then used for voxel-wise cross-subject statistics.

Finally, a posthoc region-of-interest analysis was performed. The Johns Hopkins University white matter atlas (23) was used to extract regions of interest from within each subject's DT imaging parameter maps after registration to common space as part of the standard TBSS preprocessing pipeline. Mean values of each DT imaging metric were calculated within the region of interest containing a plurality of significant voxels at the initial TBSS analysis and subsequently compared between subjects who returned to work and those who did not.

Statistical Design

Voxel-wise statistical analysis of diffusion metrics was performed by using the randomize tool in the Functional MR Imaging of the Brain software library, which employs nonparametric permutation testing based on a standard general linear model design setup (24). Threshold-free cluster enhancement was used to correct for multiple comparisons, and the threshold for statistical significance was chosen as $P < .05$ for a two-tailed test.

Demographic, clinical, and military variables were initially assessed by using

Figure 2

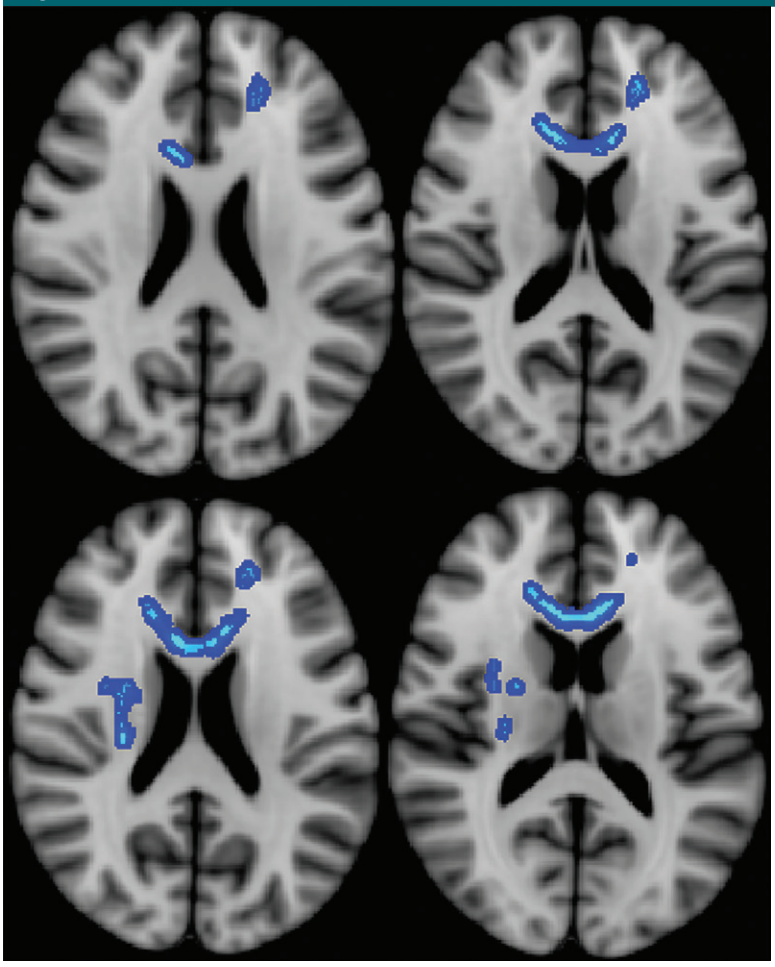

Figure 2: Results of voxel-wise correlation of FA with NSI affective cluster subscore (top row) and NSI total score (bottom row) across all subjects overlaid on axial structural images of template brain. Images show regions of inverse correlation between FA and affective subscore ($P = .042–.05$) as well as NSI total score ($P = .016–.05$) within white matter of left and right frontal lobes as well as within genu of corpus callosum (regions where lower FA is found in those with higher symptom score). Colored voxels = significant voxels after correction (dark blue, $P < .05$; light blue, $P < .045$).

Figure 3

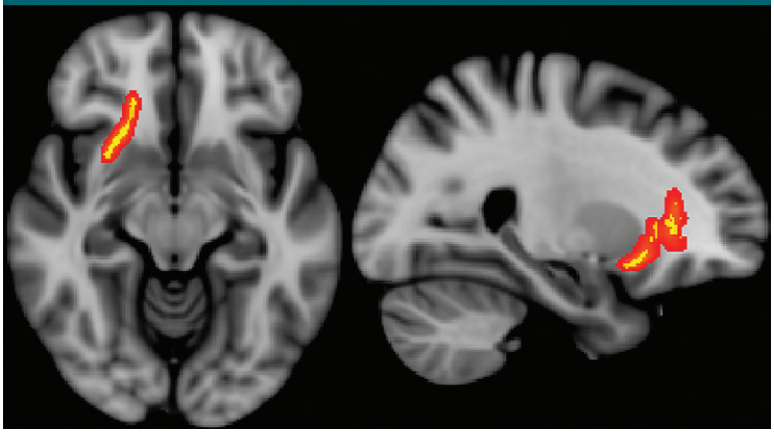

Figure 3: Results of voxel-wise correlation of FAFI with length of time since injury across all subjects overlaid on axial (left) and sagittal (right) structural images of template brain. Images show regions of direct correlation ($P = .03–.05$) within white matter of inferior right frontal lobe (regions where lower FAFI is found among those with more recent history of TBI). Colored voxels = significant voxels after correction (red, $P < .05$; yellow, $P < .04$).

a univariate voxel-wise approach. For functional outcomes, multivariate regression was used to address potential confounders. Voxel-wise comparison to occupational status at the end of follow-up and health care visits over time included nuisance variables for age, education level, time from injury, and comorbid diagnoses. These variables were selected for inclusion as nuisance variables in the regression model because they have previously been shown to affect DT imaging measurements in white matter (9,25). The regression model for health care visits over time included occupational status at follow-up as an additional nuisance variable based on the possibility that occupational status could affect access to health care. Veterans who did and who did not return to work were also compared for differences in clinical variables by using the *t* test and χ^2 test where appropriate (implemented in Microsoft Excel [Microsoft, Redmond, Wash]).

Results

Study Population

Of 76 veterans with mild TBI who had undergone DT imaging, 19 (25%) were excluded for the following reasons: less than 6 months of available follow-up data ($n = 6$), age greater than 50 years ($n = 5$), abnormal brain MR image ($n = 5$), medical comorbidity ($n = 2$), and more than 1 year between brain MR imaging and clinical evaluation ($n = 1$). For the remaining 57 subjects who met all study criteria, the mean time between injury and initial postdeployment evaluation and/or brain MR imaging was 3.8 years

(range, 0.5–9 years; standard deviation, 2.5 years). After initial postdeployment evaluation, the mean follow-up was 1.4 years (range, 0.5–2.5 years; standard deviation, 0.8 year).

Demographic, injury, and clinical characteristics of the study population are summarized in Table 1.There were no significant differences in clinical variables between veterans who returned to work during the follow-up period and those who did not (Table 2). In addition, the mean follow-up duration did not significantly differ between these two groups (1.5 years and 1.4 years, respectively). The mean NSI total score across all subjects was 39.5 (range, 11–74; standard deviation, 15.6), which corresponds to the 98th percentile in comparison with normative data obtained from a large sample of National Guard members who were deployed but did not sustain mild TBI (18).

DT Imaging and Clinical Variables

There was a significant inverse correlation between NSI score and FA within white matter of the right and left frontal lobes as well as the genu and body of the corpus callosum (Fig 2). A similar white matter distribution demonstrated an inverse correlation between FA and the affective cluster NSI subscore (Fig 2). FA values did not show correlation with other NSI subscores. Diffusivity measures and FAFI values did not show correlation with NSI scores.

There was a significant direct correlation between length of time from injury and FAFI within white matter of the inferior right frontal lobe (Fig 3). FA and diffusion values were not correlated with length of time from injury. There were no significant associations between DT imaging and clinical diagnoses of depression, PTSD, or substance abuse. Furthermore, there were no significant associations between DT imaging and injury mechanism, close blast injury, or loss of consciousness.

DT Imaging and Functional Outcomes

Of the 57 veterans included in our study, 34 (60%) had returned to work by the end of the follow-up period. Return to work was independently associated with a relative increase in FA within white matter of the posterior limb of the left internal capsule as well as the left frontal lobe (Fig 4). Furthermore, return to work was associated with a relative decrease in mean diffusivity within white matter of the left frontal lobe, left temporal lobe, left internal capsule, left parietal lobe, and right parietal lobe (Fig 4) as well as a relative decrease in the radial diffusivity within white matter of the left temporal lobe and left parietal lobe white matter (Fig 4). FAFI and axial diffusivity were not associated with return to work.

Posthoc region-of-interest analysis of the posterior limb of the left internal capsule also demonstrated significant group-wise differences in DT imaging metrics. Subjects who returned to work

Figure 4

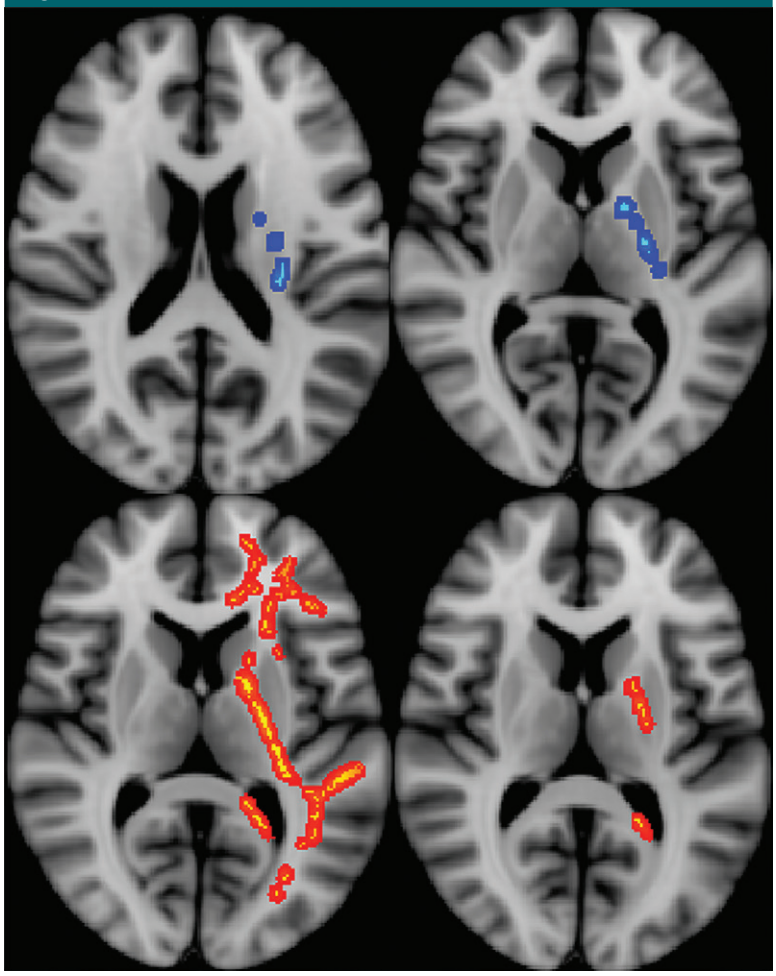

Figure 4: Results of group-wise comparison of diffusion metrics between subjects who returned to work by the end of follow-up and those who did not, controlled for age, education level, time from injury, and comorbid diagnoses. Results are overlaid on axial structural images of template brain. Regions of lower FA ($P = .02–.05$) are present within white matter of posterior limb of left internal capsule among those who did not return to work by the end of follow-up (top row). Regions of higher mean diffusivity ($P = .022–.05$) are present within white matter of left frontal lobe, left temporal lobe, posterior limb of left internal capsule, and splenium of corpus callosum (bottom left). Regions of higher radial diffusivity ($P = .04–.05$) are present within posterior limb of left internal capsule and splenium of the corpus callosum (bottom right). Colored voxels = significant voxels after correction (red or dark blue, $P < .05$; yellow or light blue, $P < .03$).

Figure 5

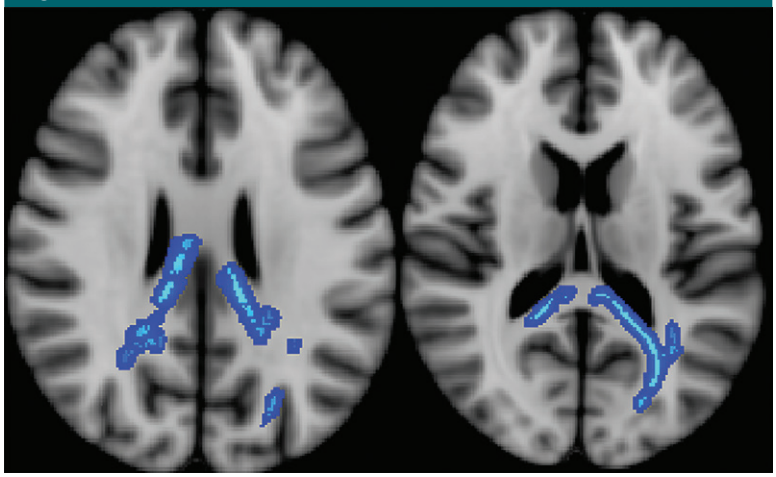

Figure 5: Results of voxel-wise correlation of FAFI with number of health care visits over time across all subjects, controlled for effects of age, education level, time from injury, comorbid diagnoses, and occupational status. Results are overlaid on axial structural images of template brain and show regions of inverse correlation (P = .026–.05) within white matter of splenium of corpus callosum, left and right parietal lobes, and left temporal lobe (regions where lower FAFI is found among those with more health care visits over time). Colored voxels = significant voxels after correction (dark blue, $P < .05$; light blue, $P < .04$).

had significantly higher FA (P = .02), as well as significantly lower mean diffusivity (P = .005) and radial diffusivity (P = .001) within the posterior limb of the left internal capsule. There were no significant regional group differences in axial diffusivity or FAFI.

The mean number of health care visits per year of follow-up in the study population was 46 (range, 3–196 visits per year; standard deviation, 41 visits per year). Health care visits over time showed an inverse correlation with FAFI in the splenium of the corpus callosum as well as within white matter of the left temporal lobe, left parietal lobe, and right parietal lobe (Fig 5). Other diffusion metrics were not independently correlated with health care visits over time.

Discussion

Among military veterans who sustained mild TBI during combat, we found significant associations between postdeployment DT imaging measurements and neurobehavioral symptoms, timing of injury, and subsequent functional outcomes. Our findings suggest that differences in white matter microstructure may partially account for the variance in functional outcomes among this population and, in particular, that loss of white matter integrity has a direct, measurable effect. Clinical measures, on the other hand, were not predictive of outcome, which suggests that imaging holds the potential to provide important and independent prognostic information at initial postdeployment medical evaluation.

This current study also provides new insight into the neurobiologic processes underlying combat-related mild TBI. Specifically, we report an association between return to work and scalar DT imaging metrics within the posterior limb of the left internal capsule, a region with previously demonstrated vulnerability to damage in mild TBI (10,11,26). Because this region is known to contain important traversing fibers that provide motor innervation to the typically dominant right side of the body, the observed association may provide a neural correlate for the clinically observed relationship between impairments in fine motor functioning and the inability to return to work after TBI (27). Several previous studies of DT imaging in combat-related mild TBI have demonstrated evidence of microstructural white matter damage manifested by reduced diffusion anisotropy and elevated diffusivity measurements in several regions, which overlaps with our results (12,28). Although previous investigations of the relationships between diffusion measurements, symptoms, and injury characteristics have resulted in mixed findings (28–30), our results are in general agreement with those that have demonstrated an association between lower diffusion anisotropy and elevated diffusivity in white matter and unfavorable functional outcomes (28,29). Our study, however, offers new information to support a similar association with longer term functional outcomes, which are of distinct importance in combat-related mild TBI. Our findings also suggest that diffusion measurements may hold predictive value, thereby providing a route by which they may become useful in a clinical setting.

This study has important limitations. In this cohort study of veterans with mild TBI, we did not have access to a comparison population of healthy subjects. This limits our results in several ways. First, our results can only be generalized to veterans with mild TBI. Therefore, although our data suggest that DT imaging has prognostic value in the setting of mild TBI, we cannot address whether DT imaging has a role in other disorders or whether DT imaging can depict mild TBI in a general population. Furthermore, although the relationship between outcomes and diffusion measurements in this study would be consistent with the effects of traumatic microstructural injury on the basis of the existing literature, the current study design does not allow this possibility to be distinguished from innate or other premorbid differences in white matter. Finally, as a retrospective study, the exclusion of subjects with incomplete data may introduce bias and limit external validity.

In conclusion, our results suggest that diffusion measurements hold the potential to confer important prognostic

information in the clinical evaluation of combat-related mild TBI. These findings should encourage continued research efforts to further refine and investigate the clinical utility of diffusion measurements in this setting. Future studies can build on this work by closely examining diffusion properties, particularly within motor pathways, and, in particular, their relationship to fine motor function and occupational outcome. In addition, further work is needed to clarify the natural history of diffusion measurements in mild TBI and the relationship between microstructural changes over time and function.

Disclosures of Conflicts of Interest: J.B.W. disclosed no relevant relationships. **R.C.B.** disclosed no relevant relationships. **E.W.** disclosed no relevant relationships. **K.M.R.** disclosed no relevant relationships. **R.J.R.** disclosed no relevant relationships. **P.G.N.** disclosed no relevant relationships.

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