Clinical and imaging assessment of acute combat mild traumatic brain injury in Afghanistan

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ABSTRACT

Objective: To evaluate whether diffusion tensor imaging (DTI) will noninvasively reveal white matter changes not present on conventional MRI in acute blast-related mild traumatic brain injury (mTBI) and to determine correlations with clinical measures and recovery.

Methods: Prospective observational study of 95 US military service members with mTBI enrolled within 7 days from injury in Afghanistan and 101 healthy controls. Assessments included Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ), Post-Traumatic Stress Disorder Checklist Military (PCLM), Beck Depression Inventory (BDI), Balance Error Scoring System (BESS), Automated Neuropsychological Assessment Metrics (ANAM), conventional MRI, and DTI.

Results: Significantly greater impairment was observed in participants with mTBI vs controls: RPCSQ (19.7 ± 12.9 vs 3.6 ± 7.1 , $p < 0.001$), PCLM (32 ± 13.2 vs 20.9 ± 7.1 , $p < 0.001$), BDI (7.4 ± 6.8 vs 2.5 ± 4.9 , $p < 0.001$), and BESS (18.2 ± 8.4 vs 15.1 ± 8.3 , $p = 0.01$). The largest effect size in ANAM performance decline was in simple reaction time (mTBI 74.5 ± 148.4 vs control -11 ± 46.6 milliseconds, $p < 0.001$). Fractional anisotropy was significantly reduced in mTBI compared with controls in the right superior longitudinal fasciculus (0.393 ± 0.022 vs 0.405 ± 0.023 , $p < 0.001$). No abnormalities were detected with conventional MRI. Time to return to duty correlated with RPCSQ ($r = 0.53$, $p < 0.001$), ANAM simple reaction time decline ($r = 0.49$, $p < 0.0001$), PCLM ($r = 0.47$, $p < 0.0001$), and BDI ($r = 0.36$, $p = 0.0005$).

Conclusions: Somatic, behavioral, and cognitive symptoms and performance deficits are substantially elevated in acute blast-related mTBI. Postconcussive symptoms and performance on measures of posttraumatic stress disorder, depression, and neurocognitive performance at initial presentation correlate with return-to-duty time. Although changes in fractional anisotropy are uncommon and subtle, DTI is more sensitive than conventional MRI in imaging white matter integrity in blast-related mTBI acutely. *Neurology*® 2015;85:219-227

GLOSSARY

ANAM = Automated Neuropsychological Assessment Metrics; **BDI** = Beck Depression Inventory; **BESS** = Balance Error Scoring System; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **FDR** = false discovery rate; **KAF** = Kandahar Airfield; **LNK** = Bastion/Camp Leatherneck; **mTBI** = mild traumatic brain injury; **PCLM** = Post-Traumatic Stress Disorder Checklist Military; **PTA** = posttraumatic amnesia; **PTSD** = posttraumatic stress disorder; **ROI** = region of interest; **RPCSQ** = Rivermead Post-Concussion Symptoms Questionnaire; **SLF** = superior longitudinal fasciculus; **SRT** = simple reaction time; **TOMM** = Test of Memory Malingering.

Blast-related mild traumatic brain injury (mTBI) has emerged as one of the most prevalent war injuries sustained by service members in the conflicts in Afghanistan and Iraq.^{1,2}

Unique features such as blast exposure, fear of imminent death, witnessing death, moral injuries, survivor's guilt, combat stress, sleep deprivation, posttraumatic stress disorder (PTSD),

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and depression³ have been increasingly recognized as significant components with potential impact on what has been considered a mild injury. As such, traditional ratings of mTBI severity including alteration and/or loss of consciousness and posttraumatic amnesia (PTA)^{4–7} may not reliably predict recovery of blast-related combat mTBI.

Diffusion tensor imaging (DTI) is an advanced MRI technique acquired on standard MRI scanners that measures water diffusion in many directions.⁸ Abnormalities on DTI are thought to reflect loss of white matter microstructural integrity, such as due to traumatic axonal injury.^{9–13}

Three MRI scanners were deployed to Kandahar Airfield (KAF), Bagram Air Force base, and Bastion/Camp Leatherneck (LNK) in Afghanistan between October 2011 and February 2013. The presence of MRI capabilities in the combat theater provided an unprecedented opportunity to study the presence and degree of white matter injury acutely in an important and understudied mTBI patient population: service members with mild blast-related injuries who recover quickly and return to duty. We hypothesized that DTI would reveal abnormalities not present on head CT and conventional MRI acutely following blast-related mTBI and that a specific pattern of injuries detected using DTI would correlate with neurologic and neurocognitive deficits and time to recovery.

METHODS Participants. Screening of 230 US active duty military service members was performed between March 2012 and September 2012 at KAF and LNK (figure 1). Service members with mTBI were eligible if they met the diagnostic criteria for mTBI as defined by the American Congress of Rehabilitation Medicine¹⁴ and sustained a blast exposure event within 7 days preceding enrollment. Controls were recruited from healthy, uninjured service members or service members receiving care for minor nonblast-related musculoskeletal injuries. Controls were eligible if they had no history of any severity TBI in the preceding 12 months. The demographic characteristics of the study participants are summarized in table 1. Reports of wartime stressors experienced by combatants were measured using the Combat Exposure Scale.¹⁵

Standard protocol approvals, registrations, and participant consents. All participants provided written informed consent before enrollment. None of the participants received monetary compensation for participating. This study was conducted under a protocol reviewed and approved by the US Army Medical Research and Materiel Command Institutional Review Board and in accordance with the approved protocol.

Clinical assessments. The median time from injury to clinical testing was 3 (range 1–8) days. All clinical assessments were conducted in a quiet, private room. Level of effort was measured using the Test of Memory Malingering (TOMM).¹⁶ Participants with TOMM score lower than 45 on 2 consecutive TOMM trials were excluded from analysis for poor testing effort (figure 1).

Postconcussive symptom severity was measured using the Rivermead Post-Concussion Symptoms Questionnaire (RPCSQ).¹⁷ Symptoms of PTSD and depression were assessed using the Post-Traumatic Stress Disorder Checklist Military (PCLM)¹⁸ and Beck Depression Inventory (BDI).^{19,20}

The neurologic examination was conducted by research staff (J.D., D.R., T.M., O.A.). Severity of balance impairment was tested using the Balance Error Scoring System (BESS).²¹

Cognitive testing was conducted using the Automated Neuropsychological Assessment Metrics (ANAM)–Traumatic Brain Injury Military version 4²² and results were compared with participants' predeployment baseline performance. Delta ANAM is defined as study ANAM minus predeployment baseline ANAM score. Poorer cognitive performance is indicated by higher ANAM scores (larger positive delta) for simple/repeat reaction time (milliseconds) and lower ANAM scores (larger negative delta) for the other modules (throughput).

Recovery time, defined as days from injury to final disposition (e.g., return to duty), was used as a surrogate for outcome.

MRI assessments. The median time from injury to MRI was 4 (range 1–8) days. All participants in both groups underwent MRI without the administration of sedation beyond that required as part of routine clinical care on Philips 1.5T Achieva scanners (Philips Healthcare, Andover, MA) at KAF and LNK. DTI was acquired using a 15-direction sequence at $b = 1,000$ with 1 b-zero image and spatial resolution of $2.5 \times 2.5 \times 2.5$ mm. To improve signal-to-noise ratio, 2 acquisitions were taken and averaged, each approximately 4:38 minutes. Conventional magnetic resonance sequences included T1-weighted ($1 \times 1 \times 1$ mm) and T2-weighted ($0.5 \times 0.5 \times 0.5$ mm) images, fluid-attenuated inversion recovery ($0.8 \times 0.8 \times 5$ mm slices), and T2*-weighted images ($1.7 \times 1.7 \times 5$ mm slices). The total scan duration for each participant was approximately 29 minutes. MRI scan data were transferred through a 4–5 relay server system via KAF and Landstuhl Regional Medical Center, Germany, to Washington University, St. Louis, for DTI postprocessing and analysis. The specifics of processing have been previously published.^{23,24} Whole-brain multiple region of interest (ROI) analysis was conducted in a semiautomated fashion using DTI Studio software.²⁵ Single individual images were aligned to a template atlas as previously published in a fully automated fashion.²⁶ DTI metrics were sampled for 130 ROIs covering the entire brain. Only white matter was compared between groups; 56 white matter ROIs were analyzed (table e-1 on the *Neurology*[®] Web site at Neurology.org). Fornix and cingulum (cingulate gyrus, hippocampus) were excluded because of insufficient spatial resolution. In addition to pure white matter structures, 4 areas of mixed white–gray matter (superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, middle frontoorbital gyrus) were included in the analysis because of their previously observed vulnerability to blast-related trauma.²⁴ In regions of mixed gray and white matter, white matter was segmented using a fractional anisotropy (FA) threshold of 0.20.

Statistical methods. All analyses were completed with Statistica 12 (StatSoft, Inc., Tulsa, OK). Primary comparison between TBI and control groups was performed using analysis of covariance, implemented using the generalized linear models tool. Age was

Figure 1 Participant screening and enrollment

A total of 230 US military service members were screened from March through September 2012 at 2 sites in Afghanistan; 212 participated, and complete data were obtained from 196 service members. CTL = controls; TBI = traumatic brain injury; TOMM = Test of Memory Malingered.

a continuous covariate, and rank (enlisted vs officer) and sex were categorical covariates.

Continuous data were screened for normality using the Shapiro–Wilk test. For variables that were not normally distributed, pairwise tests were performed using Mann–Whitney *U* tests. For normally distributed data, unpaired Student *t* tests were utilized.

Correlations were determined by Pearson product moment or Spearman rank depending on the distribution of the residuals. Correlations were repeated after trimming potential outliers as follows: first, the cases with the highest 5% and the lowest 5% values of each predictor variable were noted. Then, the cases with the highest 5% and the lowest 5% values of the outcome variable (days to return to duty) were noted. Cases in either of these groups were deleted. There was some overlap between these cases, and there were several ties, so the total trimming was not always equal to 20%.

The χ^2 or Fisher exact test was used, depending on the group size, to compare categorical data. Correction for multiple comparisons was determined by Bonferroni or false discovery rate

(FDR). Multivariate models were constructed using the generalized linear models tool. Power and sample-size calculations, performed a priori, are described in detail in the e-Methods.

RESULTS Participants. Alteration of consciousness was reported by 92 participants (97%) with mTBI. Although 53 (56%) sustained loss of consciousness, the duration was less than 5 minutes in the majority (96%). PTA (anterograde, retrograde, or both) was experienced by 35 (37%). Only 2 participants with mTBI required medical evacuation to Landstuhl Regional Medical Center. None of the participants with mTBI sustained severe injuries and only 22 (23%) reported other minor injuries (musculoskeletal, soft tissue). No trauma-related abnormalities were identified on head CT in the 68 participants with mTBI who underwent imaging as part of

Table 1 Participant characteristics

Characteristic	mTBI (n = 95)	Controls (n = 101)	p Value
Age, y			
Median	26	28	0.0002 ^a
Range	19–41	19–48	
Sex, male, n (%)	93 (98)	79 (78)	0.00001 ^b
Branch of service, n (%)			
Army	79 (83)	39 (39)	0.00001 ^b
Marine Corps	15 (16)	11 (11)	
Navy	1 (1)	39 (39)	
Air Force	0 (0)	12 (12)	
Rank, n (%)			
Enlisted	89 (94)	78 (77)	0.001 ^b
Officer	6 (6)	23 (23)	
No. of deployments ^c	2.11 ± 1.67	1.81 ± 1.26	0.24 ^a
Returned to duty, n (%)	93 (97)		
Return-to-duty time, d			
Median	7		
Range	2–26		
Returned to duty within 7 d, n (%)	54 (57)		
Combat Exposure Scale ^d	18.41 ± 9.13	5.28 ± 8.63	0.0000001 ^a
History of attention deficit disorder ^e	4	5	0.90 ^b
History of learning disability ^f	4	0	0.06 ^b

Abbreviation: mTBI = mild traumatic brain injury.

^aTwo-tailed Mann-Whitney U.

^bChi-square test.

^cControls n = 100 (data not available for 1 participant).

^dmTBI n = 94 (data not available for 1 participant).

^emTBI n = 93, controls n = 100 (data not available for 2 participants with mTBI and 1 control).

^fmTBI n = 94, controls n = 100 (data not available for 1 participant with mTBI and 1 control).

routine medical care. Women, officers, and older individuals were better represented in the control group (table 1). Group comparisons by age, rank, sex distribution, and injury-to-MRI scan days did not show any statistically significant differences between the 2 recruiting sites (table e-2).

Symptoms. The mTBI group reported significantly more intense symptoms on the RPCSQ compared with the control group (figure 2A, $F_{1,191} = 95.9$, $p < 0.000001$). Significant group differences were found across 15 of 16 individual RPCSQ symptoms (table e-3). The largest effect sizes were recorded for specific somatic symptoms (headache, dizziness, phonophobia, fatigue, and sleep disturbance) and cognitive symptoms (taking longer to think and poor concentration). Since officers, women, and older participants were better represented in the control group, the results were validated by performing demographically matched subgroup analysis using enlisted men

only (87 with mTBI and 67 controls, mean age 26 and 27, respectively, $\chi^2 p = 0.08$). The results remained statistically significant (table e-4).

Neurologic examination and balance. The neurologic examination was normal in all participants. Balance was significantly more affected in the mTBI group compared with the control group (figure 2B, $F_{1,183} = 6.1$, $p = 0.014$) with a relatively small effect size (Cohen $d = 0.37$, effect size $r = 0.18$). However, the difference lost statistical significance when analysis was restricted to subgroups of age-matched enlisted men, reflecting the reduction in group size or insufficient BESS sensitivity (table e-5).

Behavioral assessments. The mTBI group reported significantly more intense symptoms on measures of depression (figure 2C, $F_{1,190} = 24.9$, $p = 0.000001$) and PTSD (figure 2D, $F_{1,191} = 41.8$, $p < 0.000001$). These results also maintained statistical significance on subgroup analysis of age-matched enlisted men only (table e-5).

Neurocognitive testing. Changes in cognitive performance assessed using postinjury ANAM scores relative to predeployment baseline (delta ANAM) were significantly larger in the mTBI compared with the control group (figure 2, F–L). Higher positive delta ANAM means in the mTBI group compared with controls were indicative of worse performance for simple reaction time (SRT) (74.5 ± 148.4 vs -11 ± 46.6 milliseconds, $F_{1,168} = 25.9$, $p = 0.000001$, figure 2F) and repeat SRT (91.6 ± 205.4 vs 14.3 ± 118.2 milliseconds, $F_{1,168} = 10.8$, $p = 0.0012$, figure 2G). Lower negative delta ANAM means in the mTBI groups compared with controls were indicative of worse performance for processing speed (-11.4 ± 18.4 vs -0.1 ± 15.6 , $F_{1,168} = 9.1$, $p = 0.003$, figure 2H), associative learning (-3.8 ± 10 vs 4.6 ± 9.7 , $F_{1,168} = 21.0$, $p = 0.000009$, figure 2I), delayed memory (-7 ± 14.6 vs 4.4 ± 13.3 , $F_{1,168} = 16.5$, $p = 0.000076$, figure 2J), working memory (-2.5 ± 6.2 vs 2.2 ± 5.7 , $F_{1,168} = 24.6$, $p = 0.000002$, figure 2K), and visual spatial memory (-6.6 ± 14 vs 2.2 ± 10 , $F_{1,168} = 17.1$, $p = 0.000056$, figure 2L). ANAM sleep index mean reflecting changes from baseline showed that controls felt significantly more alert than participants with mTBI at the time of testing (-0.24 ± 1.05 and 0.76 ± 1.31 , respectively) (figure 2E, $F_{1,168} = 24.4$, $p = 0.000002$). These results maintained strong statistical significance on subgroup analysis of age-matched enlisted men (table e-6).

Controls and participants with mTBI were neurocognitively similar at baseline; predeployment ANAM data, available for 84 controls and 87 participants with mTBI, showed no significant differences between the 2 groups (tables e-7 and e-8).

Figure 2 More-severe concussive symptoms, depression, posttraumatic stress disorder, impaired balance, and cognitive dysfunction in participants with mTBI

(A) RPCSQ ($n = 101$ CTL, 95 mTBI, Mann-Whitney U). (B) BESS ($n = 99$ CTL, 89 mTBI: 2 CTL and 6 mTBI participants did not complete BESS because of musculoskeletal injuries, Student t test). (C) BDI ($n = 101$ CTL, 95 mTBI, Mann-Whitney U). (D) PCLM ($n = 101$ CTL, 95 mTBI, Mann-Whitney U). (E-L) Change in ANAM measures, where deltas are defined as study ANAM scores minus baseline ANAM scores ($n = 87$ CTL, 84 mTBI). (E) Sleep index; (F) SRT; (G) 2SRT; (H) processing speed, assessed with PRT; (I) associative learning assessed by CSL; (J) delayed memory assessed by CSD; (K) working memory assessed by MTP; (L) visual-spatial memory assessed by MTS. All were significant after Bonferroni correction for multiple comparisons. Dashed lines represent maximum scores. For box plot displays, boxes indicate first, second, and third quartiles, plus (+) symbols indicate means, bars indicate 5–95 percentiles, and values outside of 5–95 percentiles are shown as discrete symbols. ANAM = Automated Neuropsychological Assessment Metrics; BDI = Beck Depression Inventory; BESS = Balance Error Scoring System; CSD = Code Substitution Delayed; CSL = Code Substitution Learning; CTL = controls; mTBI = mild traumatic brain injury; MTP = mathematical processing; MTS = Matching to Sample; PCLM = Post-Traumatic Stress Disorder Checklist Military; PRT = Procedural Reaction Time; RPCSQ = Rivermead Post-Concussion Symptoms Questionnaire; SRT = simple reaction time; 2SRT = repeat SRT.

Conventional MRI and DTI findings. Conventional MRIs reviewed by a board certified neuroradiologist (J.R.) and radiologists (D.A., B.D.) identified no brain trauma-related abnormalities. Analyses of DTI data revealed univariate statistically significant reduction in FA between the injured and control groups in 6 ROIs (table e-9). After FDR correction for multiple comparisons, only the right superior longitudinal fasciculus (SLF) differed significantly between groups ($F_{1,189} = 16.9$, $p = 0.000057$, figure 3). Analysis at the single individual level demonstrated DTI abnormalities, defined as FA reductions 2 SDs below the mean for controls, in 7 participants (7%) with mTBI in the SLF. Subgroup analysis using age-matched enlisted men (DTI data available for 87 participants with mTBI and 65 controls) showed that the SLF remained statistically significant (Mann-Whitney U , $p = 0.002$, respectively), with a trend toward significance after FDR correction for multiple comparisons, likely

attributable to the reduction in sample size. Analyses of mean diffusivity, axial diffusivity, and radial diffusivity detected no significant group differences for any ROI after correction for multiple comparisons. Analysis of DTI data collected on a single individual scanned at both sites did not show any machine-dependent differences in acquisition between KAF and LNK (figure e-1).

Correlates of return-to-duty time. Clinical measures but not imaging results correlated with recovery time, defined as days required to return to duty (figure 4). Participants who reported having lost consciousness returned to duty slightly later than those who did not report loss of consciousness (figure 4A). Significant additional correlations with time to recovery were found for total symptom severity assessed by the RPCSQ score (figure 4B), change in reaction time measured by the delta ANAM SRT (figure 4C), severity on measures of PTSD assessed by the PCLM

Figure 3 Reduced fractional anisotropy on diffusion tensor imaging in the right superior longitudinal fasciculus in participants with mTBI

(A) Scatterplot of fractional anisotropy values for each participant. Solid horizontal lines represent the means and the SDs. The dotted horizontal line marks 2 SDs below the mean for CTL. Solid symbol points (triangles for mTBI, squares for CTL) represent participants below this level. (B) Diffusion tensor fractional anisotropy images displaying signal loss in the right superior longitudinal fasciculus in a participant with mTBI compared with a CTL (arrows). Images are displayed in anatomical convention. CTL = controls; mTBI = mild traumatic brain injury.

(figure 4D), and depression assessed by the BDI (figure 4E). These correlations were robust after trimming potential outliers (RPCSQ correlation: $r = 0.42$, $p = 0.0001$, $n = 76$; delta ANAM SRT correlation: $r = 0.44$, $p = 0.0002$, $n = 69$; PCLM correlation: $r = 0.41$, $p = 0.0004$, $n = 72$; BDI correlation: $r = 0.34$, $p = 0.0043$, $n = 69$). A multivariate model including all 5 of these factors predicted return-to-duty time only modestly better than any single factor (figure 4F). Alteration in consciousness, retrograde amnesia, and anterograde amnesia were not related to recovery time in participants with mTBI (figure e-2). No significant correlations were found between DTI FA in any of the examined ROI and recovery time, or with clinical variables evaluated including RPCSQ,

BDI, Combat Exposure Scale, BESS, and ANAM modules.

DISCUSSION In this study, MRI was used to prospectively acquire brain imaging data in service members with mTBI acutely in a combat zone. The absence of trauma-related changes on conventional brain MRI is likely attributed to the very mild injuries in our cohort. Nonetheless, the study demonstrates the feasibility of MRI-based research in a combat zone, despite substantial logistical challenges. Subtle drops in DTI FA in 6 of 56 brain ROIs, most notably the SLF, are suggestive of disruption of white matter integrity. The SLF has also been previously found to be affected in chronic^{27–29} as well as subacute mTBI.^{30,31} One study, however, reported that SLF changes may be associated with comorbid depression independent of mTBI in this patient population.³²

The main strength of this study is the enrollment of a unique patient population of service members exposed to concussive intensity blast in combat and a control population recruited in the same environment. Prior small-sample human blast-related mTBI studies used participants exposed to subconcussive intensity blasts as part of military training.³³ The large sample size compared with most studies examining DTI changes in mTBI was powered to detect anticipated small differences considering the very mild severity of these injuries. This study is one of the few^{34,35} that prospectively and systematically analyzed postconcussive symptoms and cognition, and the only one to our knowledge that used MRI in blast-related mTBI acutely, in the combat environment, close to the point of injury where the recovery takes place.

Nonetheless, this study has important limitations. First, the injured and control cohorts were not perfectly matched demographically, with a higher proportion of older participants, officers, and women in the control group. Analysis of covariance was used to attempt to account for these differences. Furthermore, demographically matched subgroup analyses indicated that the main results maintained statistical significance or trended toward statistical significance and thus were unlikely to have resulted from effects restricted to certain specific subgroups of participants. Even in matched subgroups, combat exposure was substantially higher in the TBI group compared with the controls and this may have affected our results. Unfortunately, it was not logistically feasible to enroll a control group with matched levels of combat exposure, and so the exact contribution of combat-related blast mTBI per se vs combat exposure as a whole cannot be resolved directly. However, in another study completed recently, combat exposure was substantially higher in evacuated US military personnel with

Figure 4 Correlates of time to return to duty

(A) LOC. (B) Total postconcussive symptom severity scored with the RPCSQ. (C) Change from baseline in simple reaction time on ANAM testing. (D) PTSD symptom severity scored using the PCLM. (E) Depression symptom severity scored using the BDI. (F) Overall prediction of return-to-duty time using a multivariate linear model including LOC, RPCSQ, ANAM, PCLM, and BDI. ANAM = Automated Neuropsychological Assessment Metrics; BDI = Beck Depression Inventory; LOC = loss of consciousness; PCLM = Post-Traumatic Stress Disorder Checklist Military; PTSD = posttraumatic stress disorder; RPCSQ = Rivermead Post-Concussion Symptoms Questionnaire.

blast-related TBI than in otherwise similar personnel with nonblast-related TBI, but clinical outcomes were indistinguishable.³⁶ Thus, combat exposure may not be the main driver of outcomes.

A second limitation was the spatial and angular resolution of the DTI scans performed, which were well below recommended standards.³⁷ Future studies of this kind may be substantially more sensitive, especially if high-resolution scans of the type being developed for the Human Connectome Project can be acquired.³⁸ Thus, the lack of correlations between DTI findings and clinical results should not be interpreted as lack of white matter structural injury in these participants.

A final limitation is that our study did not use direct outcome measures for clinical correlations but instead used time to return to duty as a surrogate. Although mTBI treatment protocols and return-to-duty decision-making in Afghanistan are well standardized, variability in patient symptom reporting and individual provider treatment styles may have distorted recovery time data.

Future longitudinal studies are needed to identify the predictive value of specific clinical, behavioral,

and neurocognitive assessments conducted in the early stages of mTBI for the subsequent development of PTSD, postconcussion syndrome, and disability. The identification of such predictive markers may help to better stratify patients early and to refine the concept of mTBI severity beyond traditional symptoms of alteration or loss of consciousness and PTA, which seem to correlate weakly or not at all with recovery time. Future studies are also needed to optimize diffusion imaging protocols and postprocessing methodology for the enhanced sensitivity needed to detect subtle white matter changes in the mildest forms of mTBI. The reversibility and clinical significance of these white matter changes will also need to be addressed in follow-up studies.

This study underscores the value of behavioral and neurocognitive assessments in addition to changes in consciousness, amnesia, and somatic symptoms when evaluating mTBI in its acute stages. This study provides important proof-of-concept data indicating that DTI has the potential to reveal disruptions of white matter integrity in specifically vulnerable brain regions. Furthermore, this study serves as a demonstration that prospective studies requiring advanced imaging

dependent on complex infrastructure and technology plus close military–civilian cooperation are feasible even in the most remote, austere, and harsh environments. The clinical significance of advanced imaging assessments remains to be fully investigated.

NOTE ADDED IN PROOF

Since acceptance of this manuscript, we have published an additional report describing 6- to 12-month outcomes and their correlates in a subset of the participants from this study.³⁹

AUTHOR CONTRIBUTIONS

Conception of design: Octavian Adam, Christine Mac Donald, David Brody, Dennis Rivet, Donald LaBarge. Acquisition, analysis, or interpretation of data: Octavian Adam, Christine Mac Donald, Dennis Rivet, John Ritter, Todd May, Maria Barefield, Josh Duckworth, Dean Asher, Benjamin Drinkwine, Yvette Woods, Michael Connor, David Brody. Drafting of the manuscript: Octavian Adam, Christine Mac Donald, Dennis Rivet, David Brody. Critical revision of the manuscript for important intellectual content: John Ritter, Todd May, Maria Barefield,

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DISCLOSURE

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Comment: Does brain DTI MRI aid diagnosis of battlefield concussion?

Traumatic brain injury (TBI) and posttraumatic stress disorder have been labeled the “signature” injuries of the wars in Afghanistan and Iraq, and the Department of Defense has invested heavily in research focused on these 2 areas. More than 327,000 TBIs, most (>82%) being mild TBIs (also known as concussions), have been sustained by active duty military service members since 2000, of which 15% occurred during deployment to a combat zone (some of the injuries were not due to combat, however).¹ Concussion is a clinical diagnosis based on history; the search for reliable objective markers (serum, imaging, balance and neurocognitive testing) is highly desirable and ongoing. In 2011, Chairman of the Joint Chiefs of Staff, Admiral Michael Mullen, directed placement of MRI scanners in Afghanistan to bring standard-of-care medicine to the battlefield. An added benefit was TBI imaging research.

This well-powered study recruited military service members with blast-related concussion who otherwise had few concurrent injuries.² A single abnormal region, the right superior longitudinal fasciculus, was identified using MRI diffusion tensor imaging at 1.5 tesla. Clinical measures of higher postconcussive and mental health symptom burden and slower reaction time were correlated (Spearman ρ 0.36–0.53) with the time to return to duty (a surrogate marker of clinical recovery). Of note, there was no correlation with duration of alteration of consciousness, loss of consciousness, or posttraumatic amnesia, questions that are asked as part of diagnosing concussion. These findings suggest that previous MRI findings in more severely injured military personnel may be due to greater injury severity.³

As with any good study, additional questions for future investigations have been generated and have broad implications for concussion management. Under what circumstances can automated neurocognitive and balance testing be relied on, since many concussed service members had performances similar to controls? Are the mental health questions applicable to a civilian concussion population? Would 3-tesla MRI have identified additional changes? This study highlights the success of the military–civilian academic partnership to conduct battlefield research and gives hope that future studies leveraging the strengths of both are feasible.

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