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White matter microstructural abnormalities in blast-exposed combat veterans: accounting for potential pre-injury factors using consanguineous controls

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Abstract

Purpose Assess the prevalence of white matter microstructural changes in combat veterans, within the context of a highly matched control group comprising unexposed close relatives.

Methods This prospective study had institutional review board approval, included written informed consent, and is HIPAA-compliant. Diffusion tensor imaging was analyzed in 16 male blast-exposed combat veterans of Operation Iraqi Freedom/Operation Enduring Freedom (mean age 31.0 years) and 18 unexposed males (mean age 30.4 years) chosen on the basis of a consanguineous relationship to a member of the subject group. Whole-brain voxel-based comparison of fractional anisotropy (FA) was performed using both group and individual analyses. Areas where effects on FA were detected were subsequently characterized by extracting radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD) from the regions of abnormal FA.

Results Controls did not differ from veterans on any background demographic factor. In voxel-based group comparison, we identify high fractional anisotropy (FA) in veterans compared to controls ($p < 0.01$). Within individual veterans, we find multiple areas of both abnormally high and low FA ($p < 0.01$) in a heterogeneous distribution, consistent with multifocal traumatic axonal injury. In individualized analyses, low FA areas demonstrate high radial diffusivity, whereas high FA areas demonstrate low RD in both group and individual analyses.

Conclusions Combat-related blast exposure is associated with microstructural white matter abnormalities, and the nature of the control group decreases the likelihood that the findings reflect underlying background differences. Abnormalities are heterogeneously distributed across patients, consistent with TAI, and include areas of low and high FA.

Keywords Mild traumatic brain injury (mTBI) · Diffusion tensor imaging (DTI) · Blast exposure

Introduction

Mild traumatic brain injury (mTBI) is the signature injury of modern warfare [1], affecting 23% of American warriors during Operation Iraqi Freedom/Operation Enduring Freedom (OIF/OEF) [2, 3]. Combat-related TBI differs from conventional impact injuries for reasons including access to care in the combat theater, prevalence of comorbid psychiatric disorders, as well as blast exposure as a unique potential mechanism of injury [4]. Understanding pathological sequelae of combat-related TBI in humans is critical to detection, diagnosis, and development of treatment.

Diffusion tensor MRI (DTI) characterizes the directional coherence (anisotropy) of water self-diffusion in tissue and is sensitive to white matter abnormalities [5]. Reduction in fractional anisotropy (FA) is the most well established DTI finding in mTBI due to conventional impact injuries [6–9], but abnormally high FA has also been seen, and bidirectional changes in FA after mTBI may be common [9]. Although FA is most commonly reported, axial diffusivity (AD), radial

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diffusivity (RD), and mean diffusivity (MD) may better characterize diffusion abnormalities related to mTBI and underlying pathomechanisms [9].

DTI abnormalities have been reported in combat-exposed veterans by comparison to control groups consisting of healthy civilians [9–12] or military veterans without prior mTBI or blast exposure [13–22]. However, there is growing concern that background subject characteristics not explicitly controlled in prior studies, such as factors occurring during a person's upbringing, may potentially confound these results [23–25]. An ideal study controlling for these factors might consist of a pair-wise comparison between identical twins both of whom serve in the military, but only one has combat experience. However, such a study design is not feasible due to the rarity of such twin pairs with differential combat exposure. Potential limitations of prior studies also include the exclusion of psychiatric conditions common in mTBI such as PTSD, depression, and substance use, which may introduce selection bias and limit the generalizability of results. Finally, analysis of DTI differences between groups limits sensitivity for detection of abnormalities. Since individuals experience trauma due to different mechanisms and with different biomechanical features, pathology in individual patients will be distributed across different locations. Group-level analyses implicitly assume pathology will be co-located across individuals and therefore cannot detect these spatially heterogeneous areas of injury and are limited to detecting injury at locations that are affected across multiple individuals. Thus, the extent of injury burden within individuals can only be assessed by examining patients individually.

The objective of this study was to assess white matter microstructural changes in combat veterans, employing controls chosen to address baseline variables such as demographic characteristics, early life experiences, socioeconomic and geographic background, as well as potential genetic factors. To do so, we utilized group-wise and individual analyses, employing a control group consisting of same sex relatives with similar demographic characteristics, early life experiences, and socioeconomic/geographic background.

Materials and methods

This prospective IRB-approved study included written informed consent and HIPAA compliance. Twenty male OIF/OEF veterans with blast-related combat exposure were enrolled between May 2013 and May 2014. We initially sought to recruit same-sex sibling controls with military experience, but not combat blast exposure. This was not achievable and we therefore enrolled as controls civilian ($n = 17$) and military veteran ($n = 3$) males without known blast or combat exposure. To maximize similarity and mitigate potential background confounders, such as demographics, socioeconomic status, and geography, controls had a consanguineous relationship (sibling or first cousin) to a veteran with whom he grew up in close proximity. Overall inclusion criteria were (a) age 18–51 and (b) English reading/speaking fluency. Inclusion criteria specific to veterans were (a) deployment within 1 year and (b) blast exposure during deployment. An inclusion criterion specific to controls was (a) same gender sibling of first cousin to a member of the veteran subject group. Overall exclusion criteria were (a) contraindication to MRI, (b) prior neurological diagnosis, (c) schizophrenia, or (d) bipolar disorder. An exclusion criterion specific to veteran subjects was history of moderate or severe TBI. An exclusion criterion specific to controls was any history of TBI. One veteran and one control could not tolerate imaging and were excluded. One control was excluded for previously unrecognized blast exposure, one veteran was excluded for other neurological disease (Parkinson's disease), and two veterans were excluded due to imaging artifacts caused by superficial embedded shrapnel. Thus, imaging was analyzed for 16 veterans and 18 controls. Although related veterans and controls were recruited as pairs, exclusions described above were not necessarily applied to both members of a veteran-control pair. Thus, in the final cohort, one veteran and three controls did not have a corresponding pair.

Demographics (Table 1), Verbal IQ (Wide Range Achievement Test), and structured clinical interview (service duration, blast exposure, acute and chronic post-concussive symptoms, prior head injury) were acquired from a computerized questionnaire independently completed by each subject (summarized in Table 1). Additional information related to service duration, blast exposure, acute and chronic post-concussive symptoms, prior head injury, military service history, and blast exposure was obtained through a structured clinical interview performed by a member of the research team. Clinical interview data could not be obtained for two veterans and four controls. Thus, where indicated, some demographic and exposure data elements are based on a subset of the full sample. Subjects were not treated at our facility, and we did not have access to their medical records.

MRI acquisition

3T MRI (Achieva TX; 32-channel Sense Head Coil; Philips Medical Systems, Best, Netherlands) included T1-weighted 3D MP-RAGE (TR/TE/TI = 9.8/4.6/1430 ms; FOV, 240 mm^2; matrix, 240 × 240; section thickness, 1 mm), T2-weighted FLAIR (TR/TE = 1100/120 ms; TI,

Table 1 Demographic information

Measure	Veterans ($n = 16$)	Controls ($n = 18$)	p
Age, mean (SD)	31.0 (5.4)	30.4 (7.2)	0.800[a]
Sex, *n* (%)			
Male	16 (100)	18 (100)	
Female	0 (0)	0 (0)	
Relationship to Control, *n* (%)[c]			
Sibling	–	10 (56)	
First cousin	–	5 (28)	
Education years, mean (SD)	14.3 (1.8)	13.8 (2.0)	0.417[a]
WRAT, mean (SD)	100.8 (10.4)	92.3 (24.9)	0.211[a]
Edinburgh Handedness Inventory, mean (SD)	81.5 (22.3)	62.7 (49.9)	0.161[a]
Employed, *n* (%)			0.070[b]
Yes	10 (62)	16 (89)	
No	6 (38)	2 (11)	
Education, *n* (%)			0.301[b]
Some high school	0 (0)	1 (6)	
High school graduate	1 (6)	5 (28)	
Some college	9 (56)	5 (28)	
Associate degree	3 (19)	4 (22)	
Bachelor's degree	2 (12)	3 (17)	
Master's degree	1 (6)	0 (0)	
Household income, *n* (%)			0.639[b]
<$10,000	1 (6)	0 (0)	
$10,000–$19,999	3 (19)	5 (28)	
$20,000–$49,999	1 (6)	3 (17)	
$50,000–$99,999	7 (44)	7 (39)	
$100,000–$299,999	4 (25)	3 (17)	
Health insurance, *n* (%)			0.458[b]
Yes	14 (88)	14 (78)	
No	2 (12)	4 (22)	
Ethnicity, *n* (%)			–
Not Hispanic or Latino	16 (100)	18 (100)	
Hispanic or Latino	0 (0)	0 (0)	
Race, *n* (%)			0.339[b]
White	16 (100)	17 (94)	
Black or African American	0 (0)	0 (0)	
Asian	0 (0)	0 (0)	
American Indian/Alaska native	0 (0)	1 (6)	
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	
Age learned English, *n* (%)			0.732[b]
English as first language	14 (88)	15 (83)	
3–5 years old	2 (12)	3 (17)	
Marital status, *n* (%)			0.361[b]
Married	11 (69)	9 (50)	
Divorced	2 (12)	1 (6)	
Separated	1 (6)	1 (6)	
Never married	2 (12)	7 (39)	
Military history, *n* (%)			<0.001[b]
Yes	16 (100)	3 (17)	

Table 1 (continued)

Measure	Veterans ($n = 16$)	Controls ($n = 18$)	p
No	0 (0)	15 (83)	
Military injury, *n* (%)			<0.001[b]
Yes	15 (94)	0 (0)	
No	1 (6)	18 (100)	
Military blast exposure, *n* (%)			<0.001[b]
Yes	16 (100)	0 (0)	
No	0 (0)	18 (0)	
*Head injuries outside of military, *n* (%)			1.000[b]
Yes	2 (17)	2 (17)	
No	12 (86)	12 (17)	
*History of contact sports, *n* (%)			0.131[b]
Yes	5 (36)	9 (64)	
No	9 (64)	5 (36)	
Medical history, *n* (%)			
Heart disease	0 (0)	0 (0)	–
Stroke	0 (0)	0 (0)	–
Diabetes	2 (12)	0 (0)	0.122[b]
High blood pressure	5 (31)	3 (17)	0.317[b]
Smoking history, *n* (%)			0.800[b]
Yes	10 (63)	12 (67)	
No	6 (38)	6 (33)	
Cigarette pack-years, mean (SD)	5.9 (7.5)	8.3 (10.6)	0.446[a]
Alcoholic drinks/week, mean (SD)	1.5 (1.4)	1.3 (1.3)	0.721[a]
Maximum alcoholic drinks/day, mean (SD)	2.7 (1.7)	2.4 (1.6)	0.594[a]
Marijuana use, *n* (%)			0.492[b]
Within past week	4 (25)	5 (28)	
Within past month	0 (0)	2 (11)	
Within past 2 months	0 (0)	1 (6)	
> 2 months ago	6 (38)	6 (33)	
Never	6 (38)	4 (22)	
Crack/cocaine use, *n* (%)			0.085[b]
Within past week	0 (0)	0 (0)	
Within past month	1 (6)	0 (0)	
Within past 2 months	0 (0)	0 (0)	
> 2 months ago	0 (0)	4 (22)	
Never	15 (94)	14 (78)	
Heroine use, *n* (%)			0.932[b]
Within past week	0 (0)	0 (0)	
Within past month	0 (0)	0 (0)	
Within past 2 months	0 (0)	0 (0)	
> 2 months ago	1 (6)	1 (6)	
Never	15 (94)	17 (94)	
Amphetamine use, *n* (%)			0.932[b]
Within past week	0 (0)	0 (0)	
Within past month	0 (0)	0 (0)	
Within past 2 months	0 (0)	0 (0)	
> 2 months ago	1 (6)	1 (6)	
Never	15 (94)	17 (94)	
LSD use, *n* (%)			0.618[b]

Table 1 (continued)

Measure	Veterans ($n = 16$)	Controls ($n = 18$)	p
Within past week	0 (0)	0 (0)	
Within past month	0 (0)	0 (0)	
Within past 2 months	0 (0)	0 (0)	
> 2 months ago	1 (6)	2 (11)	
Never	15 (94)	16 (89)	
Other drugs, *n* (%)			0.932[b]
Yes	1[d] (6)	1[e] (6)	
No	15 (94)	17 (94)	
Urine drug test at time of imaging, *n* (%)			0.595[b]
Positive	4[f] (25)	6[g] (33)	
Negative	12 (75)	12 (67)	

[a] Unpaired *t*test

[b] Chi-squared

[c] The final cohort included three controls (and one veteran) without a corresponding pair due to exclusions after subject-control pair recruitment. See methods for details

[d] One veteran reported using prescription opiates within the week prior to evaluation

[e] One control reported using prescription opiates more than 2 months prior to evaluation

[f] Three veterans had a positive urine drug test for THC, one had a positive-urine drug test for opiates, and one was positive for opiates and cocaine at the time of evaluation

[g] Six control subjects had a positive urine drug test for THC, two of whom were also positive for opiates at the time of evaluation

[*] Indicates data acquired from structured clinical interview that could not be acquired from all subjects. See Methods for details

2800 ms; FOV, 256 mm^2; matrix, 372 × 248; section thickness, 2 mm), DTI (TR/TE = 11,777/51 ms; FOV, 256 mm^2; matrix, 128 × 128; section thickness, 2 mm; 32 independent diffusion sensitizing directions; *b* value, 800 s/mm^2), 3D dual echo GRE B_0 map (TR/TE1/ΔTE = 20/2.4/2.3 ms; FOV, 256 mm^2; matrix, 64 × 64; section thickness, 4 mm; flip angle, 20°), and SWI (3D-PRESTO; FOV, 240 mm; 0.25 mm^3 voxels, TR/TE = 16/23).

Image pre-processing

All images were reviewed by, and subsequent analyses were overseen by, an ABR-CAQ neuroradiologist (M.L.L.) with 20 years of experience. Images were evaluated for gross image degradation, clinical abnormalities, or incidental findings which might preclude further analysis.

After head motion and eddy current correction, tensor fitting was performed at each voxel utilizing FMRIB Diffusion Toolbox [26] to compute fractional anisotropy (FA), axial diffusivity (AD; magnitude of principle Eigenvector), radial diffusivity (RD; mean of 2nd and 3rd Eigenvalues), and mean diffusivity (MD; mean of 1st, 2nd, and 3rd Eigenvalues) [27].

Non-brain voxels were removed from the MP-RAGE volume [28], with errors corrected manually. EPI distortion correction was performed using B_0 unwarping [29]. EPI distortion corrected images were registered to the subject's MP-RAGE volume using rigid body transformation with six degrees of freedom [30, 31].

Voxel-wise group comparison (see Fig. 1)

Template registration

Each subject's MP-RAGE volume and diffusion maps (FA, MD, AD, and RD) were registered to the Johns Hopkins University (JHU) T1-weighted template [32–34] using the non-linear Automated Registration Toolbox (ART) [35, 36].

Identification of abnormal FA clusters

A white matter mask was generated for the JHU template with the fast automated segmentation tool (FAST) within FSL. This mask was eroded using a 3-voxel kernel to limit edge effects. A general linear model (GLM) was used to compare mean FA at each white matter voxel between the subject and control groups, covarying for age and education. To control type I errors (false positives), we set a voxel-level *p* value threshold to 0.005 (single tail) and only considered FA clusters larger than 100 contiguous voxels. This corresponds to overall cluster level *p* value of 0.01 as previously reported [37].

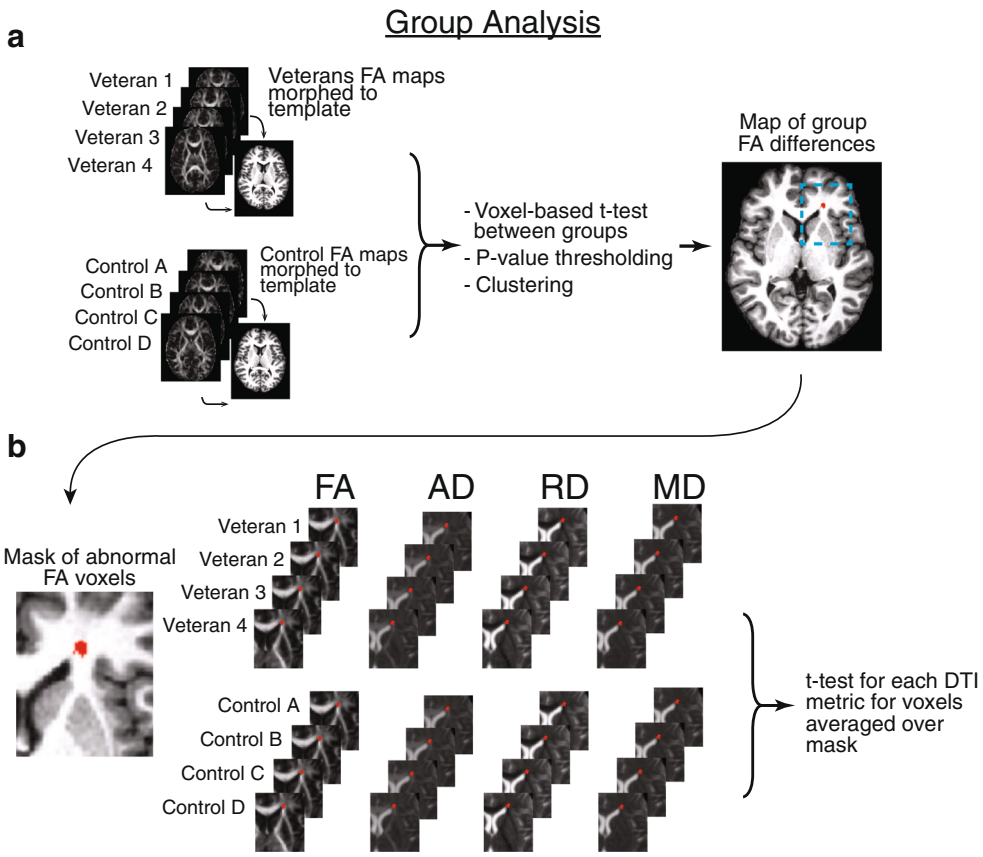

Fig. 1 Schematic for voxel-wise group comparison of diffusion measures. **a** Veteran and control FA maps are registered to a common template space, and a voxel-based analysis is then used to identify clusters where FA differs between veteran and control groups. **b** FA, RD, AD, and MD are averaged across each abnormal FA cluster in each individual veteran and subject. Student's *t* test is used determine differences in each diffusion metric between veteran and control groups

Group comparison of diffusion parameters

To further characterize group-wise diffusion abnormalities, we averaged FA, MD, AD, and RD in each subject across the voxels within the abnormal FA clusters identified in the voxel-wise group comparison (described above). This process yields four scalar measures (FA, MD, AD, and RD) for each subject, representing the mean of each value within voxels comprising abnormal FA clusters.

Voxel-wise individual subject analysis (see Fig. 2)

Inter-subject registration

For each veteran, the T1-weighted volume and all diffusion parameter maps of each control were registered to the veteran's T1-weighted volume using ART [38]. This process was repeated such that each member of the control group was registered separately to each veteran [37].

Identification of abnormal FA clusters

A separate white matter mask was generated for each veteran by applying FAST to their T1-weighted volume and eroding the mask using a 3-voxel kernel (as in the group-comparison above). For each veteran, a separate GLM was used to compare FA to the entire control group at each white matter voxel, with age and education as covariates ("one-versus-many" *t* test) [39, 40]. Only clusters ≥ 100 contiguous voxels meeting a voxel-level threshold of $p < 0.005$ (1-tail) were considered abnormal as in the group-comparison above. The anatomic location for each abnormal (high or low) FA cluster was assigned according to the automatic subcortical segmentation label assigned by FreeSurfer (below) [41, 42] for the voxel at the cluster's center of gravity.

Evaluation of diffusion parameters in individual FA clusters

For each abnormal FA cluster identified in an individual veteran, each diffusion parameter (FA, RD, AD, MD) was averaged across the voxels comprising the cluster in that veteran as well as within the homotopic voxels from each control. To facilitate comparison of the different clusters across subjects, *Z*-scores were computed for each diffusion parameter at each cluster, based on the mean and standard deviation across the control group for the given cluster.

Volumetric analysis

Brain volume and cortical thickness measurements were generated using FreeSurfer (v5.1) [42, 43]. For lobar

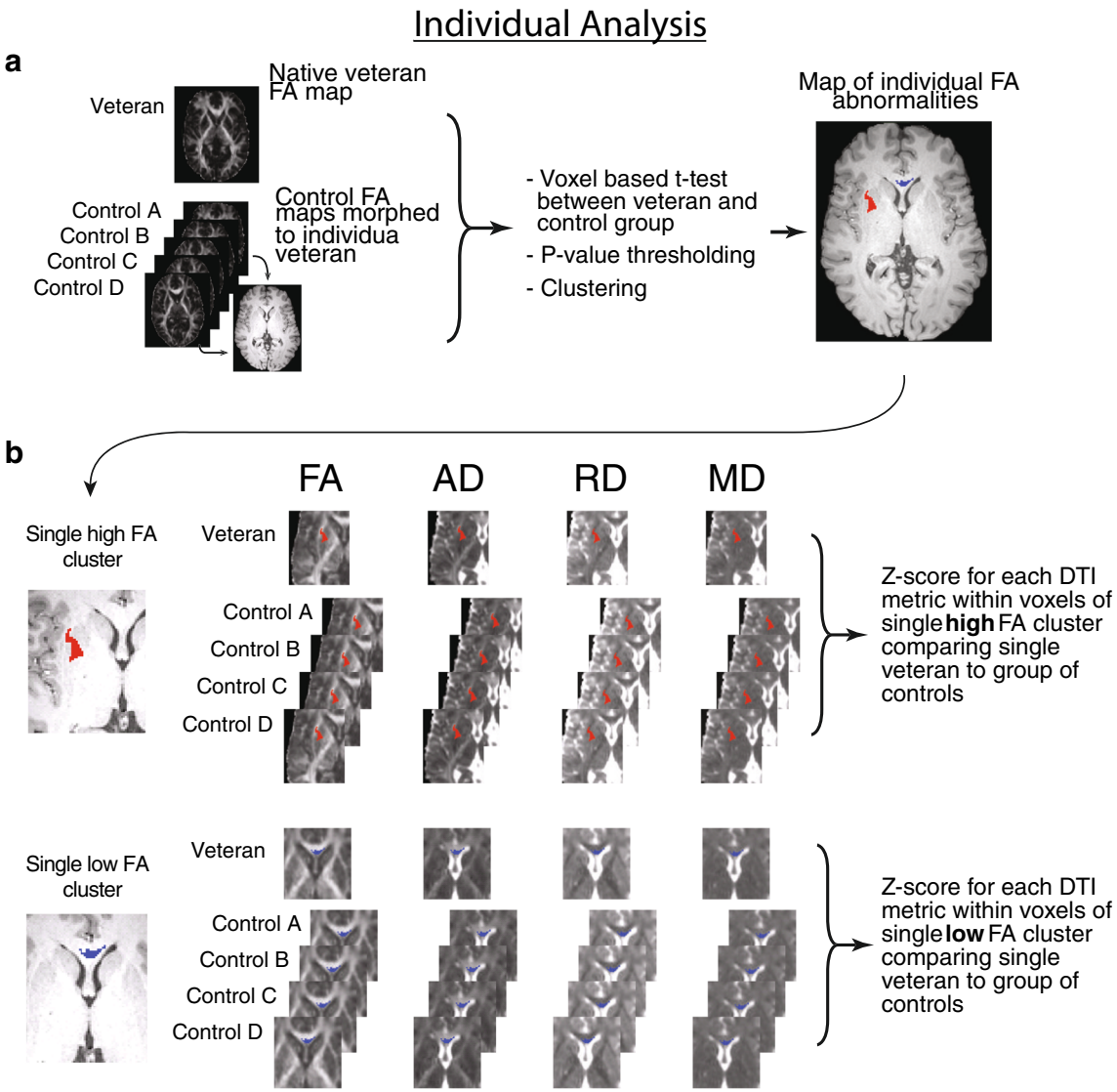

Fig. 2 Schematic for voxel-wise individual subject analysis. **a** Control subject FA maps are registered to an individual veteran and a voxel-based analysis is then used to identify clusters where FA differs between the individual veteran and the control group. **b** For a given abnormal cluster identified in an individual veteran, each diffusion parameter (FA, RD, AD, MD) is averaged across the abnormal voxels in the veteran and each control subject. A *Z*-score is calculated for each diffusion parameter by relating the veterans' diffusion parameter value to the mean and standard deviation of the control group for that cluster

measurements of cortical thickness, frontal and temporal lobes were chosen as regions most likely to be affected in TBI.

Statistical analyses

Statistical analyses were performed with SPSS (v21.0).

Results

Demographic characteristics, military history, and blast exposure characteristics for veteran subjects and controls are summarized in Table 1. Although subjects were recruited on the basis of combat and blast exposure, one veteran did not indicate a history head injury or exposure to blasts on his computerized questionnaire performed at the time of testing, which underscores that personal recollection of mTBI, especially in the complex combat theater, can be unreliable [4]. History of non-military head injury, contact sports, and all measured background and demographic characteristics were not significantly different between veteran subjects and controls (Table 1). Drug use was reported by both veterans and controls at similar rates (Table 2). Indistinguishable numbers of veteran and control subjects had positive urine drug screens at the time of imaging (Table 1); no subject or control exhibited behavioral stigmata of impairment or intoxication at the time of assessment. Additional military service details for veterans are summarized in Table 2.

Table 2 Military history for veterans

Measure	
Branch served ($n = 14$)	
Army	7 (50)
Army National Guard	6 (43)
Marine Corps	1 (7)
Deployment theater ($n = 16$)	
Iraq	12 (75)
Afghanistan	4 (25)
Tours of duty ($n = 16$)	
1	14 (88)
2	2 (12)
Deployment duration in months, mean ± SD (range)	11.4 ± 5.8 (range 3–24)
Separation status ($n = 14$)	
Completed military service	6 (43)
Separated for medical reasons	4 (29)
Separated for other reasons	2 (14)
Not yet separated from military	2 (14)
Months since separation from military, mean ± SD (range)	80.8 ± 16.6 (1.8)
VA schedule rating disabilities, mean (range)	79.2 (0–130%)

Structural MRI

Clinical image review identified evidence of superficial hemosiderin deposition suggestive of prior contusion in 12.5% (2/16) of veterans, but in no controls. Areas of nonspecific white matter hyperintensity were seen in 31% (5/16) of veterans and 5.6% (1/18) of controls. An incidental developmental venous anomaly was seen in one veteran and one control (first cousins), and a small incidental posterior fossa arachnoid cyst was seen in one veteran. At a false discovery rate of 0.05, we found no significant differences in global or regional brain volume or cortical thickness between veterans and controls (Table 3) indicating that these groups have grossly similar brain structure and volume. A larger corpus callosum size in veterans initially appeared significant ($p = 0.021$), but this differences did not survive correction for multiple comparisons.

Voxel-wise group comparison of diffusion measures

Our voxel-based comparison of FA for veteran and control groups found one 220 mm^3 cluster with center of gravity located at JHU coordinates 111, 161, 76 in the left frontal periventricular white matter where veterans demonstrated higher FA (Fig. 3a). This FA difference was further characterized by determining the average FA value across voxels comprising this cluster for each individual (Fig. 3b). A post hoc assessment of other DTI metrics within this cluster demonstrated that RD is lower in veterans by $(5.33 \times 10^{-5}) \pm 1.48 \times 10^{-5}$ mm^2/s. AD is higher in veterans compared to controls by $(4.44 \times 10^{-5}) \pm 2.46 \times 10^{-5}$ mm^2/s. MD is lower in veterans by $(2.07 \times 10^{-5}) \pm 1.44 \times 10^{-5}$ mm^2/s (Fig. 3). Thus, a greater degree of the change in FA is accounted for by RD than AD.

Voxel-wise individual subject analysis

In contrast to the single cluster of high FA identified across the group of veterans, individual veterans demonstrated a heterogeneous number and distribution of abnormal FA clusters, including clusters with abnormally low or abnormally high FA (cluster numbers for individual veterans summarized in Table 4, images from representative veterans in Fig. 4a). Individual veterans exhibited mean 2.6 (0–8; SD 2.2) abnormal FA clusters with mean total abnormal FA cluster volume 513 mm^3 (0–1938; SD 25). When considering the number of high and low FA clusters separately, individual veterans exhibited mean 0.75 (0–5; SD 1.3) low FA clusters with mean low FA cluster volume 150 mm^3 (0–1282; SD 304) and mean 1.8 (0–5; SD 1.6) high FA clusters with mean abnormally high FA cluster volume 363 mm^3 (0–1293; SD 366). Notably, 19% of veterans (3/16) demonstrated no areas of abnormal FA. Clusters of abnormal FA demonstrated spatial heterogeneity among veterans (Table 5). A single cerebellar cluster in one veteran appeared to localize to cerebellar cortex. This appearance is likely an artifact arising from small errors in transformation of the FreeSurfer label map onto the DTI statistical results. Note that all analyses are performed on FA images masked by a white matter segmentation map. Thus, all reported abnormalities arise from white matter.

To better understand the diffusion characteristics that underlie FA abnormalities, we computed a *Z*-score for each diffusion metric (RD, MD, AD) within each abnormal FA cluster (Fig. 4). We first considered the 12 low FA clusters identified across the group of individual veterans. All of these clusters demonstrated RD above the control mean. In contrast, these clusters demonstrated more heterogeneous changes in AD and MD, with clusters both above and below the control mean for these measures (Fig. 4b).

We also considered the 25 high FA clusters identified across the group of individual veterans. Almost all of these clusters demonstrated RD below the control mean. In contrast, these clusters demonstrated more heterogeneous changes in AD and MD, with clusters both above and below the control mean (Fig. 4c).

Discussion

In this study, we enrolled patients and controls with similar socio-demographic background, demonstrating white matter

Table 3 Morphometric MRI results

	Volume, cm^3, mean (s.d,)		
Brain region	Veterans ($n = 16$)	Relative controls ($n = 18$)	P
Estimated total intracranial volume	1578.1 (248.6)	1654.7 (110.1)	0.245[a]
Brain volume	1284.5 (125.1)	1332.5 (95.0)	0.580[b]
Brain volume without ventricles	1267.1 (121.4)	1314.2 (95.1)	0.575[b]
Cortex	528.9 (54.5)	520.3 (78.6)	0.356[b]
Left hemisphere Cortex	262.6 (28.3)	258.0 (41.0)	0.363[b]
Right hemisphere Cortex	266.3 (26.3)	262.2 (37.7)	0.350[b]
Cortical white matter	525.6 (70.3)	575.7 (136.8)	0.371[b]
Ventricles	15.23 (5.32)	16.50 (7.61)	0.995[b]
Subcortical gray matter	59.91 (3.70)	60.86 (3.13)	0.891[b]
Left hippocampus	4.36 (0.32)	4.37 (0.35)	0.756[b]
Right hippocampus	4.29 (0.34)	4.33 (0.30)	0.846[b]
Left amygdala	1.53 (0.17)	1.53 (0.14)	0.468[b]
Right amygdala	1.54 (0.16)	1.60 (0.16)	0.517[b]
Corpus callosum	3.73 (0.66)	3.50 (0.48)	0.021[bc]

[a] Unpaired t test

[b] Univariate analysis with estimated total intracranial volume as covariate

[c] Corpus callosum volume difference does not survive correction for multiple comparisons. No statistically significant differences detected at a false discovery rate of 0.05

microstructural abnormalities in blast-exposed combat veterans. The nature of the sample makes it less likely that the findings reflect background differences compared to a standard control group strategy using entirely unrelated controls. We demonstrate three main findings. First, we show are area of abnormal FA in a group-wise comparison of veterans vs. controls. Second, when veterans are analyzed individually, we delineate multiple areas of abnormal FA that are

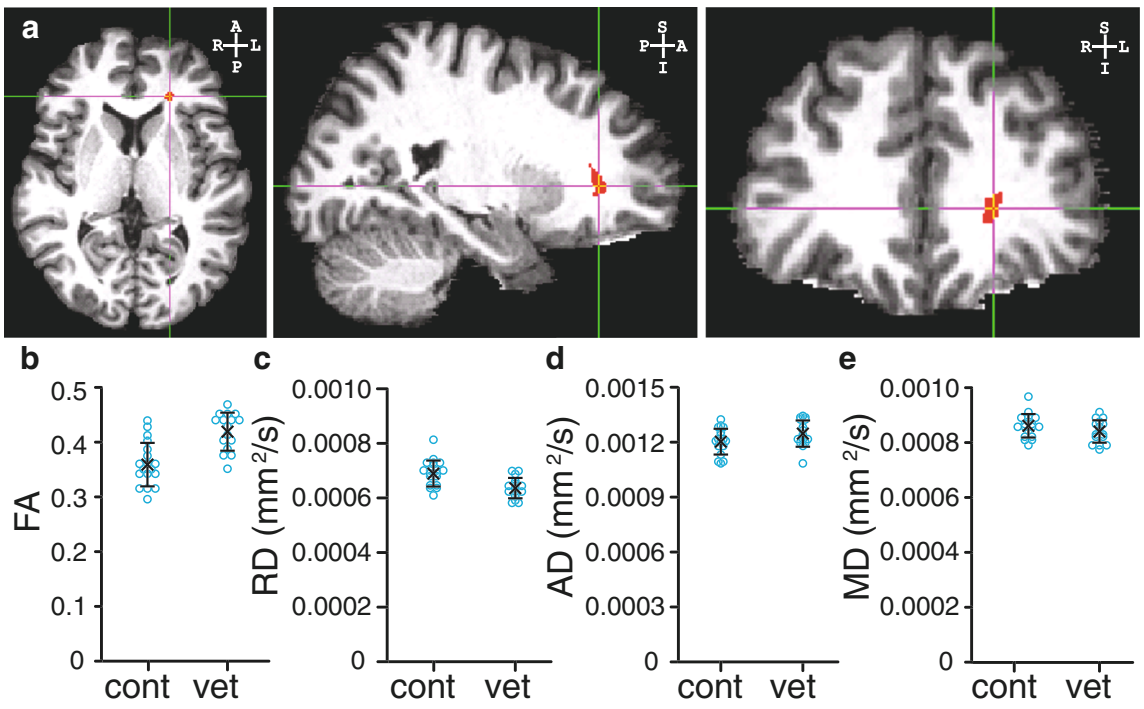

Fig. 3 DTI abnormalities in whole brain voxel-wise group analysis. **a** Axial, sagittal, and coronal orientation of standard space T1-weighted image showing location of cluster in which FA is abnormally high in veterans compared to controls. **b**–**e** Scatter plot and superimposed bar chart quantifying **b** FA, **c** RD, **d** AD, and **e** MD within the voxels of low FA demonstrated in **a** in controls (cont) and veteran (vet) groups. Circles indicate mean value for individual subjects. X indicates group mean and I bar indicates 1 standard deviation

Table 4 Number of high and low FA clusters for individual veterans

Individual veteran	High FA clusters (*n*)	Low FA clusters (*n*)
Veteran subject 1	5	0
Veteran subject 2	2	0
Veteran subject 3	1	1
Veteran subject 4	1	2
Veteran subject 5	3	5
Veteran subject 6	0	1
Veteran subject 7	0	0
Veteran subject 8	1	1
Veteran subject 9	3	0
Veteran subject 10	3	2
Veteran subject 11	0	0
Veteran subject 12	1	0
Veteran subject 13	0	0
Veteran subject 14	4	0
Veteran subject 15	4	0
Veteran subject 16	1	0

heterogeneously distributed across veterans' brains. Third, FA abnormalities are characterized more by changes in RD than in AD and MD. By matching controls with relatives, we partially address potential variation in background environments and experiences, including socioeconomic, geographic, and environmental variables not accounted for in previous analyses of DTI in combat-exposed veterans. Additionally, the biological relationship of veterans and controls plausibly addresses, in some part, additional familial/genetic variables to a degree not previously attempted in analyses of DTI in combat-exposed veterans.

We find DTI abnormalities when comparing subjects to controls using both group and individual level approaches. FA abnormalities detected in individuals are distributed heterogeneously across individual veterans, are more extensive, and are not co-localized with findings of the group-wise comparison, similar to prior reports [7, 22, 44]. Group-wise comparison may be more sensitive to small magnitude differences occurring at the same location across the group. In contrast, group-wise comparison will be less sensitive to injuries that are not co-located across individuals. Heterogeneous spatial distribution of microstructural changes is expected in TBI due to variable injury mechanism. Thus, analysis of individuals is plausibly more sensitive to spatially diverse injuries, which are expected in TBI arising from diverse biomechanical mechanisms. Many of the abnormalities we find, in subcortical white matter, corpus callosum, brain stem, and cerebellum, are similar to those identified previously [14, 19, 22, 31, 45] and support the hypothesis that certain brain structures are more susceptible to TAI. The overall burden of TAI among blast-exposed veterans, however, is variable; and in multiple veterans, our analysis did not demonstrate any FA abnormalities. This negative finding does not necessarily exclude TAI pathology in these individuals, and may be due to (1) limited sensitivity of our quantitative imaging assay to detect abnormality, (2) variable likelihood of individuals to express injury after blast exposure, and/or (3) a dose response relationship between blast exposure and detectable microstructural abnormality. Moreover, we find no significant differences (after correction for multiple comparisons) in global or regional brain volumes. This feature of our results underscores the microstructural nature of the injury pathology. Further work, including longitudinal studies of larger samples will be necessary to characterize the relationship between blast-related combat-exposure, extent of DTI abnormality, and long-term risk for loss of brain volume in veterans.

TAI is thought to disrupt microstructural barriers to diffusion with consequent decrease in diffusion anisotropy; most studies describe low FA in mild TBI [9]. We find areas of both low and high FA in individual veterans compared to controls. High FA has been reported in civilian mTBI, both acutely [46, 47] and in the chronic phase [48–50]. Similarly, the majority of reports of DTI in blast-exposed veterans describe abnormally low FA. However, high FA has been reported in blast-exposed veterans with mTBI [51] and has been associated with increased suicidal ideation and impulsivity in blast-exposed veterans [12, 52]. Increased FA in the chronic phase of mild TBI may be related to plasticity and/or reparative mechanisms, a possibility supported by animal models [53, 54]. Elucidating the substrate of high FA in blast-exposed veterans will require additional study.

FA is the most commonly reported DTI summary metric, but other metrics have been linked to unique pathological features and are of increasing interest. It is also important to note that while change in FA implies a change in some combination of the other DTI parameters, AD, RD, and MD, the nature of change of any one parameter cannot be reliably predicted from change in FA. In animal models, AD is associated with axonal damage whereas RD is associated with myelin degradation and repair [55, 56]. We find that areas of lower FA in combat-exposed veterans are primarily characterized by higher RD, similar to other reports [14, 22, 51, 57], whereas areas with higher FA are primarily characterized by lower RD. It is important to note that our assessment of diffusion metrics other than FA (RD, AD, MD) serves only to characterize the main effect on FA. FA is a summary parameter derived from the same source data that determine RD, AD, and MD. These depictions (Fig. 4) are not themselves the basis of any hypothesis testing. We do not test for group differences of these measures, which would be nonindependent [58]. Thus, the nature of our analysis does not permit us to conclude group differences between veterans and controls in measures other than FA, but only to suggest potential implications of the FA findings. Evaluation of axial

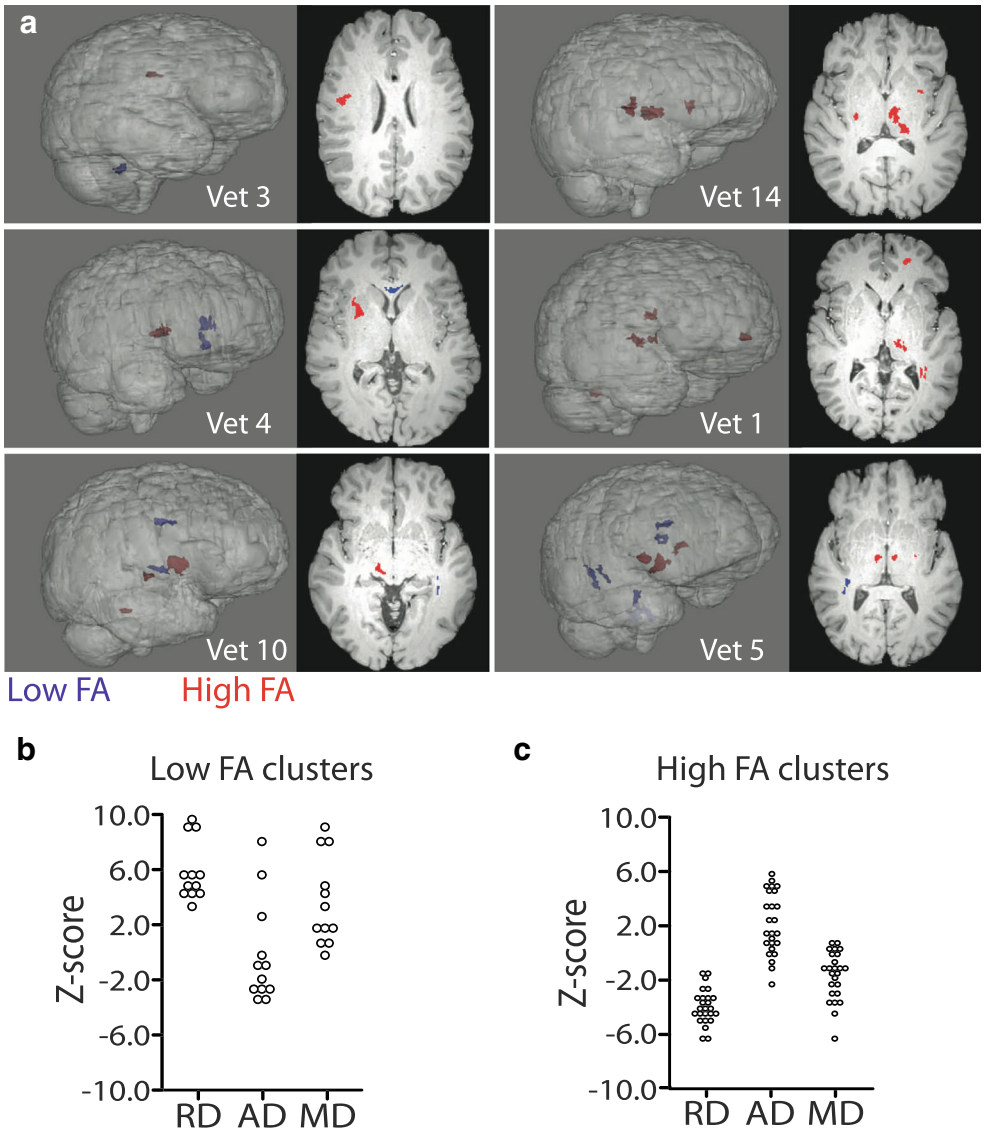

Fig. 4 DTI abnormalities in individual veterans. **a** 3D projections and representative axial slices from six representative individual veterans with low FA clusters (blue) and high FA clusters (red) superimposed on each veteran's T1-weighted image. **b**–**c** Scatter plot of *Z*-score for clusters of **b** low and **c** high FA clusters in individual veterans. Circles represent individual clusters

and radial diffusivity has not been reported in other studies reporting abnormally high FA in blast-exposed veterans. Changes in diffusion metrics must be interpreted carefully [59], but our findings suggest that remote exposure in our subjects results in persistent injury-related pathology, possibly related to myelin and axonal damage, which manifests as lower FA and higher RD. In distinct brain areas, coexistent plasticity and reparative mechanisms, perhaps including re-myelination, may manifest as increased FA and decreased RD.

Generalizability of DTI findings in blast-exposed combat veterans may be constrained by exclusion criteria applied during subject group selection. In particular, psychiatric diagnoses such as major depressive disorder (MDD), post-traumatic stress disorder (PTSD), and substance use are common among blast-exposed individuals. Moreover, these clinical syndromes may be direct sequelae of traumatic brain injury [17, 45, 52], and studies that exclude them [13–16, 18, 22] risk selection bias and insensitivity to a large subset of blast injuries in which psychiatric disease is co-morbid with or even a principle feature of TBI. Our inclusion of subjects regardless of these symptoms and diagnoses thus enhances our ability to capture a large proportion of blast-related TBI cases, although we therefore cannot conclude that DTI findings are due specifically to blast alone. Moreover, our findings are more representative of the relevant population of blast-exposed veterans in whom psychiatric symptoms and diagnoses are prevalent and may be directly due to TBI.

The relationship of diffusion abnormalities in mTBI caused by blast or other trauma to clinical dysfunction is an area of active investigation [9], and clinical significance of the diffusion abnormalities we see in veterans to clinical outcomes is an important path for future research. Importantly, imaging

Table 5 FreeSurfer subcortical segmentation labels for abnormal FA clusters in individual veterans

Brain region	High FA clusters (*n*)	Low FA clusters (*n*)
Cerebral white matter	10	7
Cerebellar white matter	2	2
Putamen[a]	5	–
Thalamus[a]	4	–
Brainstem	1	2
Ventral diencephalon	2	–
Cerebellar Cortex[b]	1	–
Corpus callosum	–	1
Total	25	12

[a] Deep gray nuclei such as thalamus and putamen contain a mixture of gray and white matter, which is accounted for in the FAST white matter segmentation (see Methods)

[b] Cerebellar cortex localization is artifactual, likely arising from small error in the transformation of the FreeSurfer label maps onto DTI results

abnormalities may be associated with current clinical dysfunction or may represent subclinical pathology that has not yet produced an overt clinical manifestation. Such subclinical findings may nonetheless confer risk for later adverse outcomes such as neurodegeneration. There is therefore need for further longitudinal study to clarify the implications of our preliminary findings.

Our findings must be interpreted in light of several limitations. First, while we attempt to address potentially confounding characteristics such as geographic, socioeconomic, and familial factors, including early life experiences, our study design did not allow control of additional potential confounding factors. It is therefore important to note that our post hoc group-wise comparison of demographic and other characteristics confirms the similarity of the groups across many known and putatively relevant characteristics, such as substance use. Moreover, later life experiences such as military service do diverge between many of our veteran and control subject pairs. Thus, we are formally limited in our ability to ascribe our findings to specific features of combat such as blast exposure, and our findings controlling for background experiences and characteristics should be viewed as a complement to previous work using military controls without mTBI or blast exposure [13–22]. In addition, because each subject was related to at most one member of the control group and the final group contained individual veterans and controls where the corresponding pair was excluded, our ability to control for genetic/familial/environmental differences is partially attenuated. It should be noted that our study uses a retrospective cohort design rather than a strictly paired analysis. Thus, our use of consanguineous controls serves to create a similar distribution of background experiences and characteristics, across the subject and control group. This approach is commonly employed to address age, education, and other factors in the absence of a true pair-matched paradigm and sample. A true pair-wise approach (ideally, perhaps, identical twins discordant for blast exposure) would better address background factors, but presents formidable technical and logistical obstacles. Thus, our approach to partially accounting potential confounding factors not previously addressed in the literature should be viewed as preliminary and motivate future study. Second, we did not exclude subjects with psychiatric diagnoses such as PTSD, MDD, and substance abuse. In particular, a history of substance use was reported and detected in both veterans and controls, although no group differences were present. While this allows us to better generalize our results to the wider population of blast-exposed combat veterans in whom stress reactions and substance use are prevalent, it may limit our ability to isolate findings to the direct effects of blast. We must, however, be mindful that isolated effects of blast on humans (as opposed to laboratory models), at any level, have not been achieved; blast effects may not in fact occur in isolation or be, alone, a clinically meaningful category of disease. Next, although the presence of nonspecific white matter hyperintensities in veteran subjects might affect our findings, the relationship between these white matter hyperintensities and diffusion changes is complex [60], and exclusion of cases with these common findings would introduce a potential source of selection bias and thereby further limit generalizability. Finally, although our sample size is small, these robust preliminary findings should serve to motivate further work in larger samples to ascertain the full scope of blast-related pathology in individual warriors.

In conclusion, our findings complement previous work by providing additional evidence for putatively combat-related spatially heterogeneous white matter microstructural changes, in the context of a related control group that addresses background characteristics and experiences to an extent not previously accounted for in the literature. In addition, our analysis of diffusion changes in individual veterans demonstrates bidirectional changes in FA that implicates coexistence of parallel underlying biomechanisms.

Compliance with ethical standards

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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