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ORIGINAL RESEARCH

White matter abnormalities are associated with overall cognitive status in blast-related mTBI

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Abstract Blast-related mild traumatic brain injury (mTBI) is a common injury of the Iraq and Afghanistan Wars. Research has suggested that blast-related mTBI is associated with chronic white matter abnormalities, which in turn are associated with impairment in neurocognitive function. However, findings are inconsistent as to which domains of cognition are affected by TBI-related white matter disruption. Recent evidence that white matter abnormalities associated with blast-related mTBI are spatially variable raises the possibility that the associated cognitive impairment is also heterogeneous. Thus, the goals of this study were to examine (1) whether mTBI-related white matter abnormalities are associated with overall cognitive status and (2) whether white matter abnormalities provide a mechanism by which mTBI influences cognition. Ninety-six Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OEF) veterans were assigned to one of three groups: no-TBI, mTBI without loss of consciousness (LOC) (mTBI-LOC), and mTBI with LOC (mTBI + LOC). Participants were given a battery of neuropsychological tests that were selected for their sensitivity to mTBI. Results showed that number of white matter abnormalities was associated with the odds of having clinically significant cognitive impairment. A mediation analysis revealed that mTBI + LOC was indirectly associated with cognitive impairment through its effect on white matter integrity. These results suggest that cognitive difficulties in blast-related mTBI can be linked to injury-induced neural changes when taking into account the variability of injury as well as the heterogeneity in cognitive deficits across individuals.

Keywords mTBI · Loss of consciousness · White matter integrity · Cognitive impairment · DTI

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Introduction

Due to the high incidence of blast-related mild traumatic brain injury (mTBI) in the Iraq and Afghanistan wars, there has been increased attention to the negative long-term consequences of blast-related mTBI, both at the neural and behavioral level. At the neural level, accumulating evidence from diffusion tensor imaging (DTI) studies suggests that blast-related mTBI is associated with changes in white matter microstructure, putatively reflecting traumatic axonal injury (Mac Donald et al. 2013; Mac Donald et al. 2011; Matthews et al. 2012; Morey et al. 2012; Hayes et al. 2015). These studies indicate that mTBI is associated with acute white matter abnormalities that persist chronically, years following the initial injury.

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At the behavioral level, blast-related mTBI has been associated with persistent cognitive difficulties (Kontos et al. 2013; Karr et al. 2014; Levin et al. 2010). Although often attributed to psychiatric comorbidities (Verfaellie et al. 2014; Campbell et al. 2009; Nelson et al. 2009; Vasterling et al. 2012; Storzbach et al. 2015; Nelson et al. 2012), cognitive impairment has also been linked to TBI-related white matter injury. However, there is inconsistency in the particular cognitive domain implicated in the association between cognitive performance and TBI-related white matter abnormality. Some studies report associations with verbal memory (Hayes et al. 2015; Levin et al. 2010), whereas others report associations with executive function (Taber et al. 2015; Jorge et al. 2012; Sorg et al. 2013).

The divergent findings in the cognitive correlates of white matter abnormalities may reflect the spatial variability of white matter injury observed in mTBI. Recent work has suggested that the location of white matter abnormalities differs from one individual to another following blast-related mTBI (Davenport et al. 2011; Jorge et al. 2012; Hayes et al. 2015; Taber et al. 2015; Miller et al. 2016). It is conceivable that the nature of the cognitive sequelae also may differ across individuals and that the cognitive profile will vary based on the pattern of neural injury. Consistent with this notion, a recent study found that individuals with mTBI who were given a battery of neuropsychological tests were more likely than would be expected by chance to have abnormal performance on two or more neuropsychological tests, even though at a group level no consistent pattern of impairment on any test was observed (Mac Donald et al. 2015). Thus, heterogeneity of cognitive impairment may be an important factor to consider when examining the impact of blast-related mTBI on neurocognitive functioning. Yet, there are currently no studies examining the association between spatially variable white matter abnormalities in mTBI and overall cognitive status.

In the present study, we examined in a large group of Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans whether spatially variable white matter abnormalities are associated with a measure of overall cognitive impairment that accommodates heterogeneity of cognitive sequelae across individuals. Building on a previous study (Miller et al. 2016) in which we found that individuals who suffered mTBI with loss of consciousness (LOC) had more spatially variable white matter abnormalities than a blast-exposed group without TBI, the goals of the current study were 1) to assess the relationship between number of white matter abnormalities and overall cognitive impairment, after accounting for posttraumatic stress disorder (PTSD) symptom severity and 2) to examine whether number of white matter abnormalities mediates the relationship between blast-related mTBI and cognitive impairment.

Methods

Participants

Ninety-six OEF/OIF veterans who reported blast exposure within 100 m participated in this study. Blast exposure included both open (e.g., dismounted in a field) and closed (e.g., in a vehicle cabin) contexts. Participants were recruited through the VA Boston Polytrauma Network and through flyers and outreach events in the community. Individuals were excluded if they had blast-induced TBI of greater than mild severity, deployment-related TBI not associated with blast, brain abnormalities (e.g., hemorrhages, hematomas) on T2-FLAIR, susceptibility weighted imaging (SWI), or T1-weighted scans as determined by a board-certified neuroradiologist, or a history of pre-deployment TBI with LOC or with symptoms persisting longer than three months post injury. High levels of current alcohol use (>25 drinks per week), and questionable effort as determined by raw scores below 45 on the retention trial of the Test of Memory Malingering (TOMM; Tombaugh and Tombaugh 1996) were additional exclusion criteria. White matter abnormalities in a subset of these participants have been described in Miller et al. (2016).

The American Congress of Rehabilitation Medicine (1993) definition of mTBI was used to assign participants to one of three groups (no-TBI, mTBI without LOC [mTBI-LOC], mTBI with LOC [mTBI + LOC]). TBI was assessed using an extensive clinical interview. First, participants were probed about their blast exposure(s) to determine the most severe event, which served as the index event. They then were asked for an in-depth description of the index event, which included events immediately preceding, during, and after the blast, to infer the presence and duration of posttraumatic amnesia, LOC, and other symptoms suggestive of TBI. Finally, participants were asked if the TBI was corroborated by a medical examination or witness. In all but three instances, information about the presence and duration of LOC for individuals in the mTBI + LOC group was based on information from a medic or peers who had witnessed the event. Two investigators evaluated all interviews, and sought consensus as to whether a biomechanical threshold for mTBI had been met and any reported disorientation was the result of mTBI.

Of the 96 blast-exposed veterans, 37 were in the no-TBI group, 31 in the mTBI-LOC group, and 28 in the mTBI + LOC group. The no-TBI group was comprised of individuals who were exposed to deployment-related blast but reported no subsequent symptoms of TBI. A subset of mTBI participants (n = 17, 14 of whom had LOC) reported having tertiary injuries (i.e., being thrown against an object or the ground resulting in additional head trauma) in addition to their blast exposure. Therefore, in this study, blast-related mTBI refers to blast mechanisms with additional tertiary injury in

some instances. A summary of the demographic characteristics can be found in Table 1.

An additional 14 veterans who were deployed in support of OEF/OIF (age, mean [standard deviation] = 30.2 [7.4]; gender, % male =71.4) formed the reference group for neuroimaging analyses. Individuals in this group reported no history of blast-exposure or deployment-related TBI, and did not meet diagnostic criteria for PTSD as assessed by the Clinician-Administered PTSD Scale (CAPS) for DSM-IV (Blake et al. 1995). Other exclusion criteria were similar to those for the other groups.

All participants underwent written and informed consent under the procedures of the VA Boston Healthcare System, Jamaica Plain campus Institutional Review Board (IRB).

Cognitive and neuropsychiatric assessments

Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler 2001). Participants were administered a battery of neuropsychological tests selected based on their sensitivity to mTBI. Table 2 provides an overview of these tests.

PTSD was assessed using the CAPS for DSM-IV (Blake et al. 1995) by a trained licensed clinical neuropsychologist. CAPS scores were used as a measure of PTSD symptom severity. CAPS scores were unavailable for three participants and were estimated based on their score on the PTSD Checklist-Military version (PCL-M; Weathers et al. 1993). Linear regression was used to generate an equation using the remaining dataset's CAPS and PCL-M scores. Then, the three individuals' PCL-M scores were entered into this equation to calculate their estimated CAPS scores.

Image acquisition and processing

All scans were collected with a 12-channel head coil at the VA Boston Healthcare System, Jamaica Plain campus on a 3-Tesla Siemens Trio MRI. An auto align scout scan was acquired before research scans were collected. Two T1-weighted three-dimensional magnetization-prepared rapid gradient-echo imaging (MP RAGE) anatomical scans were acquired for each participant. T1-weighted scan parameters for the first 28 participants were the following: FOV = 256, Matrix = 240 × 256, 160 slices, 1 × 1 × 1.2 mm voxels, TR = 2300 ms, TE = 2.98 ms, flip angle = 9°. The remaining participants were scanned with a modified sequence: FOV = 256, Matrix = 256 × 256, 176 slices, 1 × 1 × 1 mm voxels, TR = 2530 ms, TE = 3.32 ms, flip angle = 7°. DTI parameters for the first 28 participants were the following: two acquisitions of 30 directions averaged for a total of 60 diffusion weighted images, FOV = 256, Matrix = 128 × 128, TR = 8000 ms, TE = 83 ms, 2 × 2 × 2 mm voxels, b value =700 s/mm^2. A modified sequence was used for the remaining participants: one acquisition of 60 directions, FOV = 256, Matrix = 128 × 128, TR = 10,000 ms, TE = 103 ms, 2 × 2 × 2 mm voxels, b value =700 s/mm^2. The sequences were modified to align them with a separate study for data sharing. Both DTI sequences were acquired for eight reference group participants and all analyses were corrected by sequence as noted below to account for any potential sequence differences.

DTI data were analyzed with the FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu) and The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain (FMRIB) FSL software package (http://www.fmrib.ox.ac.uk/fsl). Images were corrected for motion and eddy currents and brain-extracted with BET (Smith 2002). The raw diffusion data were fitted with a tensor model using FreeSurfer to create fractional anisotropy (FA) images. Tract-Based Spatial Statistics (TBSS; Smith et al. 2006) was used to align FA images to a standard space and a threshold of 0.2 was used to restrict the white matter voxels to only white matter.

Table 1 Demographic and clinical characteristics

	no-TBI (n = 37)	mTBI-LOC (n = 31)	mTBI + LOC (n = 28)	Group Comparison
Age in years, *M (SD)*	30.2 (6.3)	29.6 (7.7)	27.9 (4.2)	$F(2,93) = 1.07$, $P = 0.35$
Males, *no. (%)*	35 (94.6)	30 (96.8)	28 (100.0)	$\chi^2(2) = 1.54$, $P = 0.46$
Education in years, *M (SD)*	13.8 (2.1)	13.0 (1.6)	12.9 (1.4)	$F(2,93) = 2.27$, $P = 0.11$
WTAR, *M (SD)*	105.0 (12.3)	107.4 (10.1)	104.6 (12.0)	$F(2,93) = 0.53$, $P = 0.59$
Blast exposures, *M (SD)*	8.4 (11.7)	11.6 (12.2)	6.2 (8.6)	$F(2,93) = 1.85$, $P = 0.16$
Injury to scan interval in months, *M (SD)*	49.8 (36.3)	43.8 (27.2)	56.3 (23.2)	$F(2,93) = 1.84$, $P = 0.17$
Current alcoholic drinks per week, *M (SD)*	4.6 (6.4)	3.4 (4.6)	4.4 (7.2)	$F(2,93) = 0.63$, $P = 0.53$
CAPS total score, *M (SD)*	48.8 (27.8)	58.4 (24.6)	63.2 (23.7)	$F(2, 93) = 2.72$, $P = 0.07$
Number of white matter hyperintensities, *M (SD)*	1.2 (2.8)	1.9 (3.9)	1.2 (3.9)	$F(2, 93) = 0.26$, $P = 0.78$

Note: For ease of interpretation, mean (*M*) and standard deviation (*SD*) reflect non-transformed data for non-normal variables. WTAR is listed as standard scores for easier interpretation

mTBI mild traumatic brain injury, *LOC* loss of consciousness, *WTAR* Wechsler Test of Adult Reading, *CAPS* Clinician-Administered PTSD Scale

Table 2 Neuropsychological tests and measures

Test	Measure
D-KEFS Trail Making Test	Number + letter sequencing, number-letter switching, motor speed
D-KEFS Verbal Fluency Test	Letter fluency total correct
D-KEFS Color-Word Interference	Color naming speed, word reading speed, inhibition
Digit Span (Wechsler Adult Intelligence Scale – III)	Digits backward score
Digit Symbol-Coding (Wechsler Adult Intelligence Scale – III)	Total correct responses
Auditory Consonant Trigrams	Total number correct averaged over 9, 18, and 36 s delays
California Verbal Learning Test	Trials 1–5 total, long delay free recall, total recognition discriminability
Brief Visuospatial Memory Test	Total recall, delayed recall, recognition discrimination index
Finger Tapping Test	Mean number of taps for dominant and non-dominant hand
Purdue Pegboard Test	Completion time for dominant and non-dominant hand

To identify clusters of abnormal FA, we used the FA standard space skeletonized images produced by TBSS to calculate z-score maps, in which each voxel was converted into a z-score based on the reference group. To correct for potential DTI sequence differences, z-score maps for data acquired with the original sequence were based on reference group participants scanned with the original sequence (n = 8), and z-score maps for data acquired with the modified sequence were based on reference group participants scanned with the modified sequence (n = 14). Z-score maps were thresholded at $z = -3.0$. For each individual, the total number of clusters with $z \leq -3.0$ in at least 5 contiguous voxels was calculated.

Statistical analysis

Statistical analyses were performed using SPSS, version 19 (IBM Corp., Armonk, NY). Age and number of clusters with reduced FA were square root transformed to account for the positive skew of the data. For similar reasons, WTAR was arcsin transformed.

To examine the association between blast-related mTBI and number of clusters with reduced FA, a hierarchical linear regression analysis was performed in which number of clusters with reduced FA was the dependent variable. Age was added as a nuisance variable in the first step of the model and mTBI group status (no-TBI, mTBI-LOC, and mTBI + LOC coded as dummy variables) was added in the second step. CAPS total score was added in the third step to examine the contribution of PTSD to clusters with reduced FA.

Next, to identify the primary domains of neuropsychological functioning and for data reduction of cognitive tests, a factor analysis with promax rotation was performed. Digit Span Backwards data was not available for 11 subjects, and there were several other instances where data on a particular test were missing for at most four subjects.[1] We used the EM algorithm with the open source program R (http://www.R-project.org) and the norm package (http://www.stat.psu.edu/~jls/misoftwa.html#aut) to impute missing data on these cognitive measures. Factor scores were estimated as z-scores using regression. Individuals were considered to have normal cognition if no z-score fell below −2. In contrast, if z-scores on one or more factor scores fell below −2, they were deemed to have evidence of clinically significant cognitive impairment. A z-score of −2 and below is generally accepted as an indicator of clinically significant cognitive impairment (Lezak 2004).

To examine the association between number of clusters with reduced FA and cognitive status, a hierarchical logistic regression analysis was performed. Age and WTAR were added as nuisance variables. CAPS total score was added into the model to account for PTSD symptoms. Lastly, number of clusters was added to determine the additional contribution of number of white matter abnormalities to cognitive impairment.

Finally, a mediation analysis was performed to examine whether number of clusters with reduced FA influenced the relationship between mTBI and cognitive status. In a mediation model, the causal variable (mTBI group) can exert an indirect effect on the outcome variable (cognitive status) through a mediating variable (number of clusters with reduced FA). Group was dummy coded so that the effect of each mTBI group could be examined with reference to the no-TBI group.

[1] Data were unavailable for Digit Span Backwards because this measure was added after initiation of the study. Several other measures were not available because of shoulder or hand injury interfering with pegboard performance (four participants), invalidity of the test due to not following instructions (one participant), or testing being completed during a follow-up session consisting of a shorter battery in which the test was not incorporated (one participant). Data were missing for five participants in the mTBI + LOC group, five participants in the mTBI-LOC group, and two in the no-TBI group.

The mTBI group not included as the independent variable was added as a covariate. Age, WTAR, and CAPS total score were also included as covariates. Direct and indirect effects were examined with the Process macro for SPSS (Hayes 2013). Bootstrapping was used to estimate the sampling distribution (n = 5000) and 95 % confidence intervals for the indirect effect.

Results

mTBI associations with white matter abnormalities

Hierarchal linear regression revealed an effect of group on number of clusters with reduced FA, with a significant overall model (R^2 = 0.13, F(3,92) = 4.69, P = 0.004) and a significant change in the model when group was added (ΔR^2 = 0.11, ΔF(2,92) = 5.57, P = 0.005). Specifically, the mTBI + LOC group had significantly more clusters with reduced FA than the no-TBI group (β = 0.36, P = 0.001; see Fig. 1). The no-TBI and mTBI-LOC groups did not significantly differ from each other (β = 0.19, P = 0.09), nor did the mTBI-LOC and mTBI + LOC groups when directly compared to each other (β = 0.20, P = 0.12). PTSD symptom severity was not associated with number of clusters with reduced FA (ΔR^2 = 0.003, ΔF(1,91) = 0.29, P = 0.60). The spatial distribution of clusters with reduced FA is shown in Fig. 2, which demonstrates that these white matter abnormalities are spatially variable across individuals and do not consistently occur in any particular location.

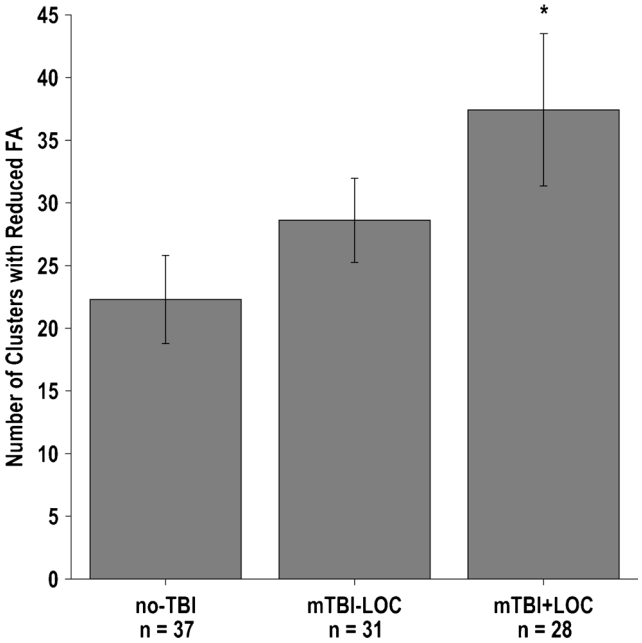

Fig. 1 Mean number of clusters with reduced FA for each group. *Note:* For interpretation purposes, figure displays untransformed number of clusters with reduced FA. * = significant group difference from the no-TBI group, P = 0.001. Error bars reflect standard error of the mean. FA=fractional anisotropy; mTBI=mild traumatic brain injury; LOC=loss of consciousness

Because a substantial number of individuals in the mTBI + LOC group also had tertiary injury, we ran an additional ANCOVA with the same covariates as above that compared mTBI + LOC participants with primary blast injury only (n = 14) to mTBI + LOC participants who sustained additional tertiary injury (n = 14). There was no significant difference in the number of clusters with reduced FA as a function of the presence of tertiary injury (F(1,24) = 2.24, P = 0.15), although numerically, there were more clusters in the group with tertiary injury (untransformed mean [standard error] = 46.7 [11.2]) than in the group with primary blast injury only (28.1 [3.7]).

Relationship between white matter abnormalities and cognition

Based on the scree plot from the factor analysis, we extracted six factors (see Table 3), which accounted for 69 % of the common variance. These factors were labeled as processing speed, verbal memory, visual memory, motor speed, working memory, and manual dexterity.

Using a measure of overall cognitive impairment based on performance in each of these domains, there were 15 individuals who met criteria for impaired cognition. Of these 15, 12 had clinical evidence for impairment in a single factor, while the remaining three had impairments in multiple factors. Figure 3 shows the number of subjects who had impairment in each factor, demonstrating that cognitive impairment was heterogeneous and did not consistently affect one particular cognitive factor.

Hierarchal logistic regression revealed an effect of number of clusters with reduced FA on cognitive status, even after accounting for PTSD symptom severity (see Table 4). PTSD symptom severity was also significantly associated with the likelihood of cognitive impairment (see Table 4).

Because odds ratios are difficult to interpret when the independent variable is transformed, we also ran a logistic regression using untransformed number of clusters. The analysis yielded a similar pattern of results and revealed that with each additional abnormal white matter cluster, individuals were 1.03 times more likely to have evidence of cognitive impairment.

Relationship between mTBI, cognition, and white matter abnormalities

A mediation analysis revealed that mTBI + LOC indirectly influenced cognitive status through its effect on the extent of white matter abnormalities, after accounting for PTSD symptom severity (see Fig. 4). Individuals in the mTBI + LOC group had a greater number of clusters with reduced FA

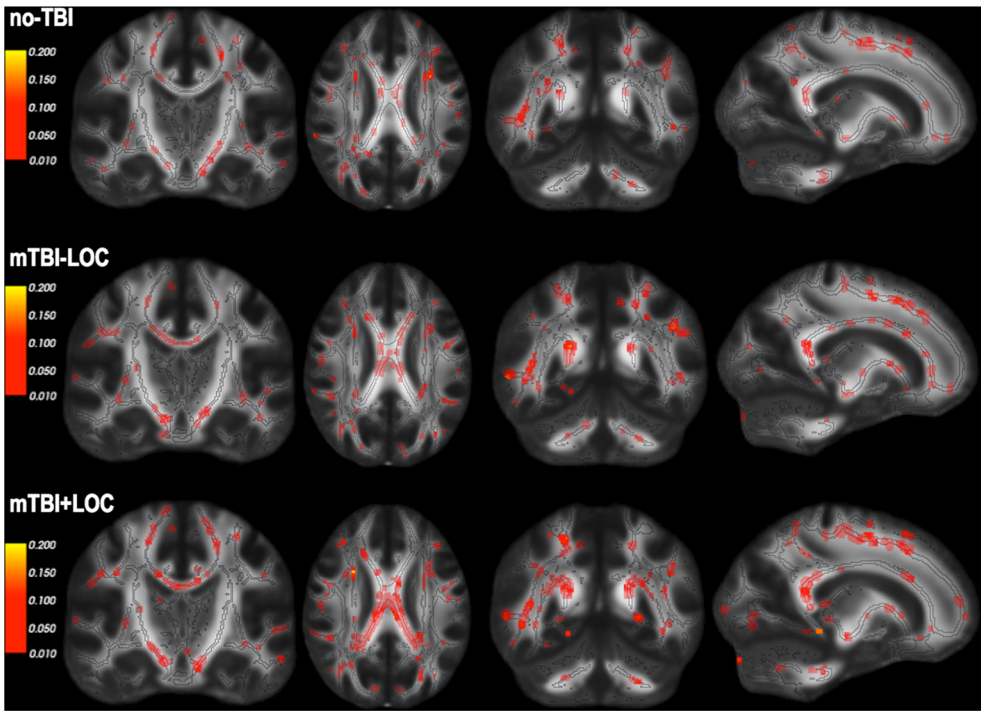

Fig. 2 Distribution of white matter clusters with reduced FA within groups. Scale indicates the proportion of individuals within each group that have a cluster of reduced FA in the area marked. FA=fractional anisotropy; mTBI=mild traumatic brain injury; LOC=loss of consciousness

(a = 1.63, $P = 0.001$), and, in turn, number of abnormal clusters was significantly associated with cognitive status (b = 0.40, $P = 0.02$). The direct effect of mTBI + LOC on cognitive status was not significant ($P > 0.5$). A bias-corrected bootstrap confidence interval for the indirect effect of cognitive impairment did not encompass zero (ab =0.66, 95%CI [0.03, 1.8]). As

Table 3 Factor loadings

	Factors					
Neuropsychological Tests	Processing Speed	Verbal Memory	Visual Memory	Motor Speed	Working Memory	Manual Dexterity
Trails number letter switching	**.843**	.091	.074	-.018	-.192	-.097
Trails letter + number sequencing	**.683**	.142	.153	.077	-.032	-.097
Verbal fluency	**.670**	.032	-.114	-.137	.136	-.103
Stroop color + word naming	**.424**	-.050	-.157	.294	**.398**	-.092
Stroop inhibition	**.386**	.102	-.078	.165	.299	.218
Consonant trigrams	-.224	.071	.208	.117	**.769**	-.098
Digit span backwards	.079	-.075	-.009	-.258	**.830**	-.097
Digit Symbol-Coding	**.361**	-.036	.050	-.079	**.417**	.342
CVLT total trials 1–5	.099	**.891**	-.130	-.125	.100	.026
CVLT delayed recall	.133	**.864**	.039	.005	-.020	-.079
CVLT delayed recognition	-.116	**.908**	.079	.049	-.104	.102
BVMT-R total trials 1–5	.169	-.099	**.842**	-.115	.031	.109
BVMT-R delayed recall	.207	-.011	**.852**	-.017	-.003	-.075
BVMT-R delayed recognition	-.307	.141	**.610**	.133	.190	-.035
Trails motor speed	**.754**	-.153	.096	.109	-.102	.080
Finger tapping dominant	.180	.010	-.043	**.853**	-.152	-.036
Finger tapping non-dominant	-.082	-.062	.020	**.914**	-.006	.038
Grooved pegboard dominant	.111	.028	-.004	-.065	-.228	**.859**
Grooved pegboard non-dominant	-.234	.021	.007	.068	.042	**.894**

Note: Factor loadings >0.35 for each test are shown in bold

CVLT California Verbal Learning Test, *BVMT* Brief Visuospatial Memory Test

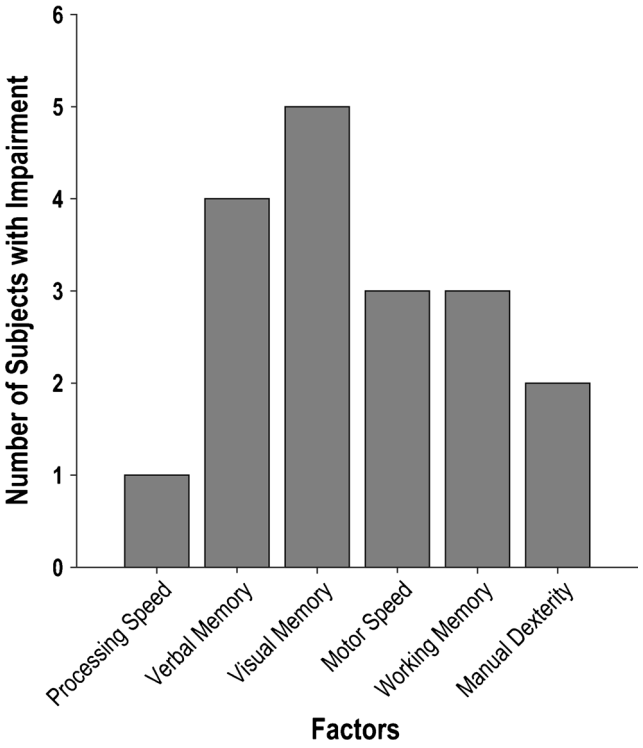

Fig. 3 Number of subjects who had impairment in each factor. *Note:* three subjects had impairment on more than one factor

expected, the extent of white matter abnormalities was not a significant mediator for mTBI-LOC.

Discussion

To our knowledge, this is the first study to examine the association between spatially variable white matter abnormalities and overall cognitive status in individuals with a history of blast exposure. Using a voxel-wise cluster-based technique in a large cohort of OEF/OIF veterans, we found that, consistent with our previous study (Miller et al. 2016), individuals with mTBI and LOC had a significantly greater number of white matter abnormalities than individuals without mTBI. Importantly, we found that these spatially variable white matter abnormalities were associated with a measure of overall cognitive impairment that accommodates variable patterns of cognitive deficiency across individuals. Additionally, number of white matter abnormalities indirectly influenced the relationship between mTBI with LOC and the likelihood of having clinically significant cognitive impairment.

Our results revealed that cognitive impairment was heterogeneous, with impairment seen across a range of factors in different individuals. These results support recent work by Mac Donald et al. (2015) who found evidence for impairment at the individual subject level in veterans with blast-induced mTBI despite lack of consistent impairment at the group level. Our findings go beyond this work in demonstrating that cognitive impairment defined at the individual subject level was associated with the neural sequelae of blast injury. Specifically, as the number of abnormal white matter clusters increased, the odds of cognitive impairment also increased.

Whereas previous studies have examined the link between global white matter disruption and performance in specific cognitive domains (Taber et al. 2015; Hayes et al. 2015), here we took into account not only heterogeneity of neural injury but also heterogeneity in cognitive impairment across individuals. The finding that cognitive impairment, regardless of its specific nature, could be linked to diffuse white matter injury is in keeping with the notion that blast-related neural injury has direct consequences for cognition. However, given the heterogeneity of cognitive impairment, such associations may not be consistently observed in any particular domain.

Table 4 Logistic regression for cognitive impairment

	Model 1			Model 2			Model 3		
Variable	*B*	SE *B*	e^B	*B*	SE *B*	e^B	*B*	SE *B*	e^B
(Constant)	0.55	3.13	1.74	-0.82	3.34	0.44	-1.31	3.41	0.27
Age	-0.39	0.59	0.68	-0.41	0.61	0.66	-0.73	0.64	0.48
WTAR	-7.01	3.56	0.001	-7.42*	3.79	0.001	-8.76*	3.91	<0.001
CAPS total score				0.02*	0.01	1.03	0.03*	0.01	1.03
Number of abnormal clusters							0.38*	0.17	1.46
Negelkerke R^2	0.08			0.15			0.24		
Model χ^2 (df)	4.50 (2)			8.69 (3)*			14.63 (4)**		
Block χ^2 (df)	4.50 (2)			4.19 (1)*			5.94 (1)*		

Note: *indicates significance $P < 0.05$; ** indicates $P < 0.01$; Age is square root transformed; WTAR is an average z-score and is arcsin transformed; Number of abnormal clusters is square root transformed

SE standard error, e^B odds ratio, *CAPS* Clinician-Administered PTSD Scale, *WTAR* Wechsler Test of Adult Reading

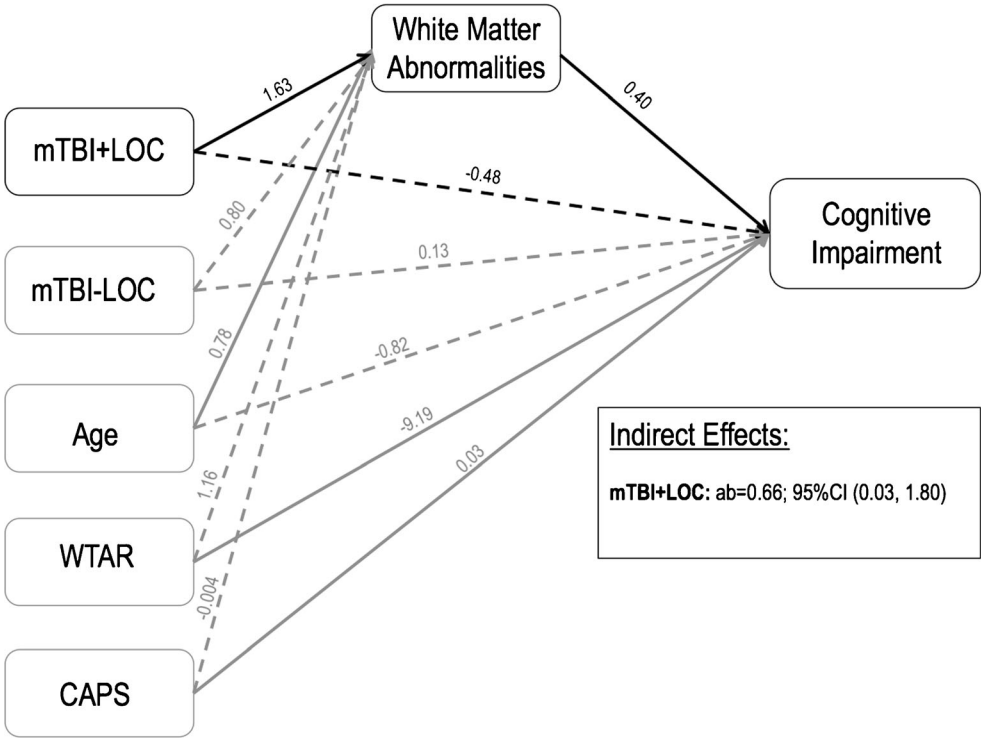

Fig. 4 mTBI + LOC indirectly influences the likelihood of having cognitive impairment through its effect on number of clusters with reduced FA. Numbers shown represent unstandardized coefficients. Solid lines indicate significance ($P < 0.05$). Gray indicates covariates in the model. FA=fractional anisotropy; mTBI=mild traumatic brain injury; LOC=loss of consciousness; CAPS=Clinician-Administered PTSD Scale; WTAR=Wechsler Test of Adult Reading

Further, we demonstrated that number of white matter abnormalities indirectly influences the relationship between blast-related mTBI with LOC and cognitive status. Specifically, as white matter abnormalities accumulate in individuals with blast-related mTBI with LOC, the odds of having cognitive impairment increases, even after taking PTSD into account. These results suggest that heterogeneous cognitive sequelae in our sample reflect to some degree mTBI-related injury. Importantly, we showed that cognitive impairment in blast-related mTBI with LOC is associated with mTBI-related white matter abnormalities when both the variability of injury and heterogeneity of cognitive impairment are considered. Our findings suggest that blast-related mTBI is a heterogeneous injury, producing unique patterns of brain injury and associated cognitive sequelae for each individual.

Because a considerable number of individuals in the mTBI + LOC group had additional tertiary injury, the question arises whether the effect of LOC on white matter abnormalities and its association with cognitive status may be due to the combined effect of blast plus tertiary injury. There was no significant difference in the number of abnormal clusters as a function of injury mechanism in individuals with LOC, although numerically there were more clusters in the subgroup of individuals with LOC who suffered additional tertiary injury. Previous studies have found no evidence for differential white matter abnormalities (Hayes et al. 2015) or cognitive deficits (Kontos et al. 2013) associated with primary injury versus combined primary and tertiary injury. More conclusive evidence will require future studies with sufficiently large samples to allow examination of the orthogonal effects of additional tertiary injury and LOC.

Another consideration in interpreting our findings relates to the effect of white matter hyperintensities, which are common in OEF/OIF veterans with TBI (Riedy et al. 2016). There is evidence that these hyperintensities are associated with enhanced white matter abnormalities (Lange et al. 2014) as well as with impaired cognition in TBI (Bigler 2006; Clark et al. 2016). It remains unclear whether these white matter hyperintensities are directly related to the trauma, or instead may reflect pre-existing differences or differences caused by other medical factors that arise after the injury. Therefore, we opted not to exclude participants based on the presence of white matter hyperintensities. Importantly, there were no group differences in the number of white matter hyperintensities, suggesting that the greater number of white matter abnormalities in the mTBI with LOC group, and its association with cognitive status, are unlikely to reflect an artifact of the presence of white matter hyperintensities.

Consistent with previous studies suggesting that mental health, including PTSD, is an important contributor to neuropsychological performance (Verfaellie et al. 2014; Hayes et al. 2015; Nelson et al. 2012; Vasterling et al. 2012; Campbell et al. 2009), we found that PTSD symptom severity was also significantly associated with cognitive status, such that as PTSD symptom severity increased, the likelihood of having cognitive impairment increased. However, PTSD was not associated with white matter abnormalities, a finding that is consistent with several other studies (Jorge et al. 2012; Morey et al. 2012; Taber et al. 2015; Miller et al. 2016). It will be important for future studies to determine

whether PTSD-related neuropathology is a mediator in the relationship between PTSD and cognitive impairment.

Our findings provide a conservative estimate of the effect of blast-related mTBI, as individuals in the control group who were exposed to blast may have experienced subconcussive events in the absence of TBI symptoms. Recent evidence suggests that blast exposure not associated with TBI may be associated with alterations in both structural (Bazarian et al. 2012; Taber et al. 2015) and functional (Robinson et al. 2015) connectivity. Thus, future studies would benefit from the inclusion of a non-blast exposed control group in addition to a blast-exposed group without mTBI to investigate the distinct contributions of blast exposure and mTBI.

Limitations of the current study should be noted. Similar to previous studies of post-deployment health, mTBI group assignment was based on retrospective self-report years after the injury occurred and may be subject to misremembering or reporting bias. However, participant reports were guided by an in-depth structured clinical interview, which is the gold standard for diagnosis (Corrigan and Bogner 2007). Another limitation was the small sample size of the reference group for neuroimaging analyses. This group required strict inclusionary criteria including absence of blast exposure and deployment-related TBI or current PTSD. Finally, the use of two imaging sequences may have added variability to the data and reduced power to detect group differences.

In summary, we report a greater number of spatially variable white matter abnormalities in individuals with blast-related mTBI with LOC in comparison to individuals without mTBI. Importantly, these white matter abnormalities were directly associated with overall cognitive status that takes into account heterogeneity across individuals. PTSD symptom severity was also associated with cognitive status, but it was not related to white matter abnormalities. The heterogeneity in neural injury as well as in cognitive impairment is an important consideration in examining brain-behavioral correlations in blast-related mTBI.

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Conflict of interest Danielle R. Miller, Jasmeet P. Hayes, Ginette Lafleche, David H. Salat, and Mieke Verfaellie declare they have no conflict of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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