Military blast exposure, ageing and white matter integrity

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Mild traumatic brain injury, or concussion, is associated with a range of neural changes including altered white matter structure. There is emerging evidence that blast exposure—one of the most pervasive causes of casualties in the recent overseas conflicts in Iraq and Afghanistan—is accompanied by a range of neurobiological events that may result in pathological changes to brain structure and function that occur independently of overt concussion symptoms. The potential effects of brain injury due to blast exposure are of great concern as a history of mild traumatic brain injury has been identified as a risk factor for age-associated neurodegenerative disease. The present study used diffusion tensor imaging to investigate whether military-associated blast exposure influences the association between age and white matter tissue structure integrity in a large sample of veterans of the recent conflicts ($n = 190$ blast-exposed; 59 without exposure) between the ages of 19 and 62 years. Tract-based spatial statistics revealed a significant blast exposure $\times$ age interaction on diffusion parameters with blast-exposed individuals exhibiting a more rapid cross-sectional age trajectory towards reduced tissue integrity. Both distinct and overlapping voxel clusters demonstrating the interaction were observed among the examined diffusion contrast measures (e.g. fractional anisotropy and radial diffusivity). The regions showing the effect on fractional anisotropy included voxels both within and beyond the boundaries of the regions exhibiting a significant negative association between fractional anisotropy and age in the entire cohort. The regional effect was sensitive to the degree of blast exposure, suggesting a ‘dose-response’ relationship between the number of blast exposures and white matter integrity. Additionally, there was an age-independent negative association between fractional anisotropy and years since most severe blast exposure in a subset of the blast-exposed group, suggesting a specific influence of time since exposure on tissue structure, and this effect was also independent of post-traumatic stress symptoms. Overall, these data suggest that blast exposure may negatively affect brain-ageing trajectories at the microstructural tissue level. Additional work examining longitudinal changes in brain tissue integrity in individuals exposed to military blast forces will be an important future direction to the initial findings presented here.

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Abbreviations: : CAPS-IV = Clinician Administered PTSD Scale, Version 4; DTI = diffusion tensor imaging; PTSD = post-traumatic stress disorder; TBI = traumatic brain injury; TBSS = Tract-Based Spatial Statistics; TRACTS = Translational Research Center for TBI and Stress Disorders; YB-blast = years between most severe blast exposure and imaging

Introduction

There has been a great deal of concern by clinicians and scientists about the apparent proliferation of brain injuries affecting veterans who have returned from the recent conflicts in Iraq and Afghanistan (Okie, 2005; Warden, 2006; Hoge *et al.*, 2008; Owens *et al.*, 2008; Wojcik *et al.*, 2010; Mac Donald *et al.*, 2011). Many of these injuries are the result of exposure to blast forces of high energy (Okie, 2005; Warden, 2006; Owens *et al.*, 2008; Wojcik *et al.*, 2010; Mac Donald *et al.*, 2011) particularly from improvised explosive devices that have been commonly used in these conflicts (Okie, 2005; Owens *et al.*, 2008). Since advances in armour and other defensive technologies made most of these explosions survivable (Okie, 2005), an unprecedented number of American and coalition combatants have returned to civilian life with histories of concussion(s) and multiple exposures to the forces resulting from these powerful explosions (Okie, 2005; Warden, 2006; Champion *et al.*, 2009). While the effects of mild traumatic brain injury (TBI), or concussion, have been studied in both a civilian (Guskiewicz *et al.*, 2005; De Beaumont *et al.*, 2009; Stern *et al.*, 2011; Bazarian *et al.*, 2012; Kerr *et al.*, 2012; Moretti *et al.*, 2012; Sivanandam and Thakur, 2012; Tremblay *et al.*, 2013, 2014) and military context (Warden, 2006; Cernak and Noble-Haesslein, 2010; Mac Donald *et al.*, 2011; Stern *et al.*, 2011; Goldstein *et al.*, 2012; Bazarian *et al.*, 2013; McKee and Robinson, 2014), the independent effects that exposure to high energy explosions may have on the CNS (Taylor and Ford, 2009; Mac Donald *et al.*, 2011; Davenport *et al.*, 2012) merit further investigation (Taber *et al.*, 2006).

Although a causative link has not been established, both the civilian and military literature on TBI suggest that a history of brain trauma may be associated with enduring changes in brain structures, especially in the cerebral white matter (Kinnunen *et al.*, 2011; Mac Donald *et al.*, 2011, 2014; Wada *et al.*, 2012; Bazarian *et al.*, 2013; Morey *et al.*, 2013; Tremblay *et al.*, 2014; Taber *et al.*, 2015). It has been shown that moderate or severe TBI is associated with an increased risk for late life dementia (Shively *et al.*, 2012; Gardner *et al.*, 2014), and that a history of concussion is a risk factor for degenerative disease in later life (Bower *et al.*, 2003; Fleminger *et al.*, 2003; Chen *et al.*, 2007), including dementia of the Alzheimer's type (French *et al.*, 1985; Fleminger *et al.*, 2003; Sivanandam and Thakur, 2012). Others have suggested that multiple concussions or even subconcussive events, such as those experienced in contact sports, may predispose some individuals to develop a unique pattern of pathology based on increased

levels of tau deposition (Omalu *et al.*, 2011; Stern *et al.*, 2011; Goldstein *et al.*, 2012; Small *et al.*, 2013; McKee and Robinson, 2014). Athletes involved in high impact sports also show evidence of disproportionate cortical thinning and lateral ventricle enlargement, neurometabolic imbalance (Tremblay *et al.*, 2013), abnormal cerebral blood perfusion, (Hart *et al.*, 2013), decreased white matter integrity (i.e. fractional anisotropy) (Hart *et al.*, 2013; Tremblay *et al.*, 2014), as well as accelerated motor and cognitive function decline (De Beaumont *et al.*, 2009; Moretti *et al.*, 2012) beyond what is observed with ageing in otherwise comparable peers. Some of the changes to white matter are similar to those that have been described as occurring with ageing (Nomura *et al.*, 1994; Courchesne *et al.*, 2000; Nusbaum *et al.*, 2001; Salat *et al.*, 2005a, b; Burzynska *et al.*, 2010; Westlye *et al.*, 2010; Lebel *et al.*, 2012) suggesting that a history of blunt head trauma may exacerbate any pathological burden typically associated with the ageing process. It is not known if trauma due to blast forces is associated with any similar phenomena.

There has been much speculation that exposure to blast forces can also inflict injury on CNS structures even without the presence of the overt clinical symptoms at the time of the event that are criteria for mild TBI (Hoge *et al.*, 2008). Although there have been some data based on animal models and on simulations with inanimate materials or computer models to support the claim that blast exposure *per se* can damage neural tissue (Kaur *et al.*, 1995; Cernak *et al.*, 2001; Bauman *et al.*, 2009; Desmoulin and Dionne, 2009; Taylor and Ford, 2009; Goldstein *et al.*, 2012) only recently have data emerged documenting possible blast-based brain changes in combat-exposed veterans (Bazarian *et al.*, 2013; Robinson *et al.*, 2015; Taber *et al.*, 2015). One of the largest studies to show that blast exposure alone can alter brain physiology was conducted by Robinson *et al.* (2015), who demonstrated that non-concussive insults associated with exposure to close-range blast(s) are equal to concussive events in their effect on brain function. The present study used diffusion tensor imaging (DTI) and a cross-sectional design in a veteran sample varying in age from 19 to 62 years to glimpse whether exposure to high intensity blast forces has effects on the integrity of cerebral white matter across the lifespan.

DTI is an established technique capable of probing white matter tissue properties by measuring the directional coherence of water diffusion in brain tissue (Le Bihan *et al.*, 1986, 1988, 2001; Basser *et al.*, 1994a, b; Basser and Pierpaoli, 1996; Le Bihan, 2003; Assaf and Pasternak, 2008). DTI is sensitive to the anisotropic diffusion found

in the structured white matter microenvironment and allows for the calculation of various diffusion parameters that can elucidate certain aspects of local brain tissue health (Le Bihan *et al.*, 1986, 2001; Basser *et al.*, 1994b; Le Bihan, 2003). Several prior studies have used diffusion imaging procedures to investigate trends in white matter integrity associated with healthy ageing (Nomura *et al.*, 1994; Courchesne *et al.*, 2000; Nusbaum *et al.*, 2001; Salat *et al.*, 2005a, b; Burzynska *et al.*, 2010; Westlye *et al.*, 2010; Lebel *et al.*, 2012) and various maladies (Molko *et al.*, 2002; Bartzokis, 2004; Bartzokis *et al.*, 2004a, b; Rosas *et al.*, 2006; Wang *et al.*, 2006; Menke *et al.*, 2012; Kochunov *et al.*, 2014) including TBI (Kraus *et al.*, 2007; Kennedy *et al.*, 2009; Kinnunen *et al.*, 2011; Mac Donald *et al.*, 2011; Bazarian *et al.*, 2012; Davenport *et al.*, 2012; Wada *et al.*, 2012; Morey *et al.*, 2013; Tremblay *et al.*, 2014) and blast-exposure (Davenport *et al.*, 2012; Bazarian *et al.*, 2013; Taber *et al.*, 2015). The aims of the present study were 2-fold: first to examine whether military blast exposure was associated with altered cross-sectional age trends in cerebral white matter integrity in a population of Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn Veterans (with or without a diagnosis of concussion or mild TBI), and second to determine whether years between most severe blast exposure and imaging (YB-blast) played a role in predicting white matter integrity, suggesting a neurodegenerative process.

Materials and methods

Participants

Two hundred and fifty-six veterans and service members characterized for blast exposure and several other military-associated factors were imaged as part of the core assessment at the Translational Research Center for TBI and Stress Disorders (TRACTS), a Veterans Affairs Rehabilitation Research and Development supported TBI Center of Excellence at VA Boston Healthcare System. This sample was drawn from 350 participants consecutively enrolled into the TRACTS Center of Excellence who were eligible for MRI and successfully underwent the diffusion imaging sequence ($n = 280$). Twenty-four of those with diffusion data could not be included because their data for one or more of the modelled covariates were not available. Participants had been or would be deployed on at least one Operation Enduring Freedom, Operation Iraqi Freedom, and/or Operation New Dawn tour and were recruited throughout the Boston Metropolitan area through outreach at Yellow Ribbon and other military-associated events. Individuals were excluded from enrolling in the TRACTS assessment if they met any of the following criteria: (i) history of neurological illness (Huntington's, Parkinson's, dementia etc.); (ii) history of seizure disorders unrelated to head injury; (iii) current diagnosis of schizophrenia, bipolar, or other psychotic disorder; (iv) self-reported severe depression or anxiety requiring hospitalization overnight, or current active homicidal and/or suicidal ideation with intent requiring crisis intervention; (v) cognitive disorder due to general medical condition other than TBI; and (vi)

unstable psychological diagnosis (suspected psychotic or personality disorder) that would interfere with accurate data collection, determined by consensus of at least three doctoral-level psychologists. The research was compliant with the Code of Ethics of the World Medical Association (Declaration of Helsinki) and the standards established by the VA Boston Healthcare System's Institutional Review Board. All participants provided informed consent prior to their participation in the study.

Assessment of military blast exposure and mild TBI

In sum, 256 veterans and pre-deployed service members were analysed. Participants were divided into two groups based on their history of blast exposure. The blast-exposed group was comprised of 195 individuals who reported that they had experienced an explosive blast at a distance <100 m during any of their deployments. The blast-unexposed group was comprised of 61 individuals who reported experiencing no blasts at any distance <100 m during any of their deployments. Note that participants in the blast-exposed group were not necessarily diagnosed with a TBI (69% with, 31% without) and some participants in the blast-unexposed group did have TBI history (53% with, 47% without).

TBI and blast history were evaluated by a psychologist using the Boston Assessment of TBI-Lifetime (BAT-L; Fortier *et al.*, 2013). TBI diagnosis was ultimately decided via consensus meeting of at least three doctoral-level psychologists. The majority of TBIs experienced by the sample were mild, defined as a loss-of-consciousness lasting <30 min, and/or an altered mental status lasting <24 h and/or a period of post-traumatic amnesia lasting <24 h.

The BAT-L is unique in its assessment of blast exposure injuries (Fortier *et al.*, 2013). The BAT-L queries two different aspects of blast: (i) number of exposures to blasts within 100 m; and (ii) number of TBIs due to blast. With regard to blast exposures, their frequency at incremental distances (≤ 10 m, 11–25 m, 26–100 m) were queried in detail and recorded. These data were used to determine the blast distance profile of the blast-exposed group.

Motivated by recent results demonstrating a specific effect of close-range blast exposure on brain function (Robinson *et al.*, 2015), the influence of YB-blast on white matter was investigated in an exploratory analysis for a subset of participants, all with close-range blast exposure ($n = 76$). For this subset, substantial information about the details of their three most severe blast exposures was catalogued and used to calculate their YB-blast.

Further participant characterization

The current (previous 30 days) presence and severity of post-traumatic stress disorder (PTSD) were assessed using the Clinician Administered PTSD Scale-IV (CAPS-IV; Blake *et al.*, 1995). The reliability and validity of this assessment tool are well documented (Blake *et al.*, 1995) and symptoms measured by CAPS-IV are associated with other brain measures including cortical thickness (Lindemer *et al.*, 2013). Alcohol consumption is another common comorbidity of PTSD and TBI that can affect grey and white matter structure

(Fortier *et al.*, 2011, 2014). Therefore, the influence of alcohol consumption on measures of interest was examined using the Lifetime Drinking History scale (Skinner and Sheu, 1982).

A number of other secondary analyses were conducted to assess the effects of potential confounders related to conditions that are often comorbid in individuals with a history of TBI (Lippa *et al.*, 2015). These were defined as follows: depression, anxiety and stress scores were defined using the Depression Anxiety Stress Score (Nieuwenhuisen *et al.*, 2003); pain score was defined using the McGill Pain Questionnaire (Melzack, 1975); and sleep quality was defined using the Pittsburgh Sleep Quality Index (Buysse *et al.*, 1989). Participants were asked to identify whether they currently use anti-depressant, pain, or sedative/hypnotic medications.

FreeSurfer was used to compute an estimate of white matter lesions from T₁ data, which are highly correlated with T₂ and have been used in several prior publications (Jacobs *et al.*, 2013; Leritz *et al.*, 2014). When used, the exclusion threshold for white matter signal abnormalities was >1%.

Neuroimaging

DTI acquisition used a 2 mm isotropic, 60 direction single shot echo planar sequence with a twice-refocused spin echo pulse sequence, optimized to minimize eddy current-induced image distortions (Reese *et al.*, 2003) [10 T₂ (b = 0) + 60 diffusion directions; b = 700, repetition time = 10 000 ms, echo time = 103 ms; bandwidth = 1395 Hz/px, slice thickness = 2.0 mm, field of view = 256 × 256 mm; 128 × 128 matrix; 64 slices; with 0 gap; automatically acquired in the AC–PC plane; total acquisition time 12:12 min]. The 60 diffusion-weighted directions were obtained using the electrostatic shell method (Jones *et al.*, 1999), resulting in a high signal-to-noise volume. The diffusion tensor was calculated on a voxel-by-voxel basis using conventional reconstruction methods (Basser *et al.*, 1994b; Fiechl *et al.*, 1999; Smith *et al.*, 2004; Andersson *et al.*, 2007a, b).

DTI preprocessing

Diffusion data were preprocessed using a multistep procedure involving the FreeSurfer image analysis suite (<http://surfer.nmr.mgh.harvard.edu/>) and FSL Diffusion Toolbox (<http://www.fmrib.ox.ac.uk/fsl/>). The raw DTI data were motion and eddy corrected using FSL, requiring the acquisition of a T₂-weighted structural volume, which was collected using identical sequence parameters as the directional volumes with no diffusion-weighting (b0 volume) and therefore in registration with the final diffusion map. This b0 volume was then used as an affine and rigid body registration target for eddy current and motion correction of the raw DTI data, respectively (Jenkinson *et al.*, 2002). FreeSurfer was then used to fit a tensor model to the corrected images. The diffusion images were brain extracted using ‘brain extraction toolkit’, a feature of FSL (Smith *et al.*, 2004).

Data were then prepared for statistical analysis using Tract-Based Spatial Statistics (TBSS) (Smith *et al.*, 2006), distributed as part of FSL (Smith *et al.*, 2004). Briefly, TBSS coregisters the data using ‘FNIRT’ (Andersson *et al.*, 2007a) to a fractional anisotropy template in standard space (Smith *et al.*, 2006) and then applies a skeletonization procedure using the

FMRI58 fractional anisotropy skeleton template provided by FSL. For each subject, the fractional anisotropy skeleton template is filled by locating voxels nearby to the skeleton with maximum fractional anisotropy (i.e. from the centre of the nearby white matter tract) (Smith *et al.*, 2006). TBSS was used for the voxel-based analysis of all diffusion-derived measures. Fractional anisotropy, a scalar metric encoding the directional coherence of water diffusion within a voxel and commonly used as an indicator of white matter integrity (Basser and Pierpaoli, 1996), was the primary diffusion-derived measure employed here to make inferences about white matter microstructure. Apparent diffusion coefficient, radial diffusivity, and axial diffusivity were also examined.

Motion analysis

Head motion during the DTI acquisition was considered because it can introduce a bias in the derived measures of diffusion (Yendiki *et al.*, 2013). Three rotation and three translation parameters from each DTI acquisition were obtained using FSL’s ‘FLIRT’ of each brain volume to the first b0 volume (Jenkinson *et al.*, 2002). To acquire a summary measure of motion, the root-mean-square of the six parameters was calculated for each volume relative to the preceding volume and averaged over all volumes of the scan. Participants were excluded from subsequent analyses for having motion scores greater than the mean motion score plus two standard deviations of all participants.

DTI analysis

‘Randomise’ (Winkler *et al.*, 2014), a non-parametric permutation testing method for statistical analysis that avoids assumptions about the distribution of DTI data, was used to perform voxel-wise analyses of the white matter skeleton and determine the significance level for the contrast of interest in the full model with covariates (clinical/demographic regressors) at every skeleton voxel using 5000 permutations. For more details about non-parametric permutation testing with regressors in neuroimaging (see Nichols and Holmes, 2001; Winkler *et al.*, 2014).

Multiple comparisons issues associated with calculating statistics for many voxels simultaneously were corrected using threshold-free cluster enhancement (Smith *et al.*, 2006, 2009; Winkler *et al.*, 2014). Threshold-free cluster enhancement takes the raw output statistic image from ‘randomise’ and produces an image in which the voxel-wise values incorporate the amount of ‘cluster-like local spatial support’ of nearby voxels. For more information on threshold-free cluster enhancement, see Smith and Nichols (2009).

The white matter skeleton voxel-wise analyses with the following covariates are included in this report: gender, education, alcohol use (Lifetime Drinking History score), and PTSD symptom severity (CAPS-IV score). To investigate the possibility of differing brain-ageing trajectories between groups, the slope of the diffusion parameter with age was allowed to differ between groups and the resulting regression coefficients were investigated for significant differences between blast-exposed and blast-unexposed groups.

Regional level analysis of interaction between age and blast exposure on fractional anisotropy

Further analyses were conducted at the regional level, using regions defined both anatomically and statistically. Anatomically-based regions are reported based on the labels of a merged FreeSurfer white matter parcellation/Johns Hopkins University white matter label atlas, with the Johns Hopkins University atlas getting precedence over the FreeSurfer-derived white matter labels in regions of overlap (Fischl *et al.*, 2002; Hua *et al.*, 2008; Salat *et al.*, 2012). The thresholded ($P < 0.05$; corrected) statistical maps were used to define the boundaries of significant clusters. These clusters were then segmented according to the merged atlas so that every cluster was subdivided into anatomically defined regions.

The custom atlas resulting from the anatomical segmentation of significant clusters was deprojected to every subject's native space and used to extract mean fractional anisotropy for each region of interest from native space (Smith *et al.*, 2006). Mean fractional anisotropy was investigated as a function of age for each region using MATLAB (Mathworks). Linear and quadratic models were used to fit a relationship with age. MATLAB was also used to perform an ANCOVA of the blast exposure $\times$ age interaction on mean fractional anisotropy in each of these anatomical segments. These analyses included the same covariates that were included in the white matter-skeleton voxel-wise analysis in addition to blast exposure by covariate interaction of the nuisance regressors (Lifetime Drinking History score, CAPS-IV score, gender, years of education). Additionally, the entire cohort after motion exclusions was analysed together using 'randomise' (FMRIB Centre, Oxford, UK) to define a region showing a significant ($P < 0.05$; corrected) fractional anisotropy association with age and this region was similarly deprojected and analysed.

Matched regression analysis of fractional anisotropy and YB-blast

To further examine the hypothesis that blast exposure initiates a neurodegenerative process, the role of time elapsed since most severe blast event was examined in participants with close-range (0–10 m) blast exposure. A control peer group was selected by matching blast-unexposed individual with a blast-exposed peer, based on age (± 5 years) and CAPS-IV (± 10 points), resulting in 34 matched pairs. Members of the blast-unexposed group were assigned the value for YB-blast of their blast-exposed match. In each group, the association between fractional anisotropy and YB-blast was compared regionally. The same covariates as the primary analysis were included when determining significance of the association between mean fractional anisotropy and YB-blast.

Results

Participant characterization

Seven participants were excluded for excessive motion, defined as $>0.64 \text{ mm}^2$ motion score, during the DTI

acquisition. Five of these participants were in the blast-exposed group and two were in the blast-unexposed group, leaving final group sizes of 190 and 59, respectively. Results of a *t*-test revealed mean motion score did not differ significantly between final groups ($P = 0.5$).

Demographic information (years of education, age, and gender) and clinical statuses (CAPS-IV score and Lifetime Drinking History score) that were included in primary analyses are detailed in Table 1. Results of *t*-tests revealed a significant ($P < 0.01$) difference in CAPS-IV score between the blast-exposed and blast-unexposed groups but not in age, years of education, or lifetime drinking history score. Pearson's chi-squared analyses revealed no significant difference in gender between the two groups. Note that overall, 90% of participants were male and 95% were post-deployment. Other potential confounders that were analysed in secondary analyses are also included in Table 1.

In the blast-exposed group, 132 (~69%) participants had at least one TBI of any type in their lifetime and 58 (~31%) had no history of TBI. Of those in this group with TBI history, 71 had a history of multiple TBI, and 51 experienced at least one blast TBI. Approximately 96% of those participants with TBI in the blast-exposed group had mild TBI only ($n = 6$ with moderate or severe). The distance profile of blasts for members of the blast-exposed group is presented in Fig. 1.

In the blast-unexposed group, 31 (53%) reported a TBI in their lifetime, nine had history of multiple TBI, none had history of moderate or severe TBI, and (by definition) none of these TBIs were due to exposure to blast forces.

TBSS and regional analysis of the interaction between age and blast exposure on diffusion parameters

TBSS analyses revealed a significant blast-exposure $\times$ age interaction on fractional anisotropy, with the blast-exposed group exhibiting a more negative relationship between fractional anisotropy and age compared to the blast-unexposed group throughout the cerebral white matter. There were also regions in which apparent diffusion coefficient and radial diffusivity showed significant differences in their association with age between blast-exposed and blast-unexposed groups. These two measures exhibited a significantly greater increase with increasing age in the blast-exposed group compared to the unexposed group. No significant interaction was observed for axial diffusivity. A map of the voxels that demonstrated a significant interaction for the three diffusion measures is presented in Fig. 2.

Notably, this finding is in contrast to similar analyses investigating a TBI $\times$ age interaction on diffusion measures. When participants were grouped based on history of TBI rather than by history of blast exposure, no significant interactions were observed ($P > 0.7$; corrected). Analyses contrasting those with two or more TBI with those with less than two TBI again yielded no significant findings for

Table 1 Group demographics for all variables included in primary and secondary analyses of white matter diffusion parameters.

	Total (n = 249)	Blast-exposed (n = 190)	Blast-unexposed (n = 59)	P-value
Primary analyses				
Age	31.88 (8.41)	31.72 (7.99)	32.39 (9.71)	0.595
Gender (M/F)	226/23	175/15	51/8	0.640
Education (years)	13.78 (1.81)	13.70 (1.77)	14.05 (1.94)	0.195
LDH total ^a	7.87 (10.59)	8.33 (10.99)	6.40 (9.15)	0.224
CAPS-IV	45.27 (29.10)	49.81 (28.09)	30.93 (27.57)	<0.001
Secondary analyses				
TBI (y/n)	163/86	132/58	31/28	0.160
Number of TBI	1.48 (2.19)	1.7 (2.42)	0.78 (0.97)	0.005
DASS Depression ^b	7.44 (8.67)	8.03 (9.21)	5.59 (6.42)	0.061
DASS Anxiety ^b	5.50 (7.04)	6.19 (7.39)	3.34 (5.28)	0.007
DASS Stress ^b	11.38 (9.25)	12.13 (9.37)	9.00 (8.50)	0.024
McGill Pain ^b	27.30 (25.20)	28.36 (25.52)	24.09 (24.15)	0.268
PSQI ^b	9.19 (4.61)	9.67 (4.64)	7.63 (4.16)	0.033
Medications				
Anti-depressant (%)	18.90	21.10	11.90	0.160
Pain (%)	25.70	26.30	23.70	0.726
Sedative/hypnotic (%)	5.20	5.30	3.40	0.467

Values are reported as mean (standard deviation) unless indicated otherwise. Bold indicates significant difference between groups. DASS = Depression Anxiety Stress Score; LDH = Lifetime Drinking History; PSQI = Pittsburgh Sleep Quality Index.

^aValues divided by 1000.

^bData not available for all participants that were included in primary analysis (n = 235–247).

any of the examined diffusion measures ($P > 0.09$; corrected).

In addition to the presented results, numerous minor changes were made to the model to account for other potential confounders. The effect was largely insensitive to inclusion of gender, alcohol use, years of education, or CAPS-IV as covariates, which were used in the presented results. Neither the substitution of sleep quality, depression, anxiety, stress, or pain score, for CAPS-IV nor the addition of covariates for anti-depressive, pain, or sedative/hypnotic medication use could account for the results presented. The results were also insensitive to inclusion of number and/or history of TBI as covariates or exclusion of participants with moderate or severe TBI. One individual had white

matter signal abnormalities comprising $>1\%$ total white matter volume and exclusion of this individual strengthened the effect.

Voxel-wise correlation between fractional anisotropy and age was calculated across both groups using TBSS to define a region of interest. The relationship between mean fractional anisotropy and age in this region is shown in a scatter plot (Fig. 3B) with linear and quadratic trend lines. The results of an ANCOVA revealed a significant blast exposure $\times$ age interaction on mean fractional anisotropy in this region ($P < 0.05$). This region is also depicted in Fig. 3A and C in both representative 2D slices and in a 3D map, where it is compared to regions demonstrating the significant voxel-wise blast exposure $\times$ age interaction on fractional anisotropy ($P < 0.05$; corrected). It can be seen that regions of the interaction largely fall in regions with age effects.

Linear and quadratic models of mean fractional anisotropy as a function of age in a representative region of interest of the custom atlas are presented in Fig. 4 to visualize the differing cross-sectional lifespan trajectories of fractional anisotropy between groups. These data represent the mean fractional anisotropy in the segmentation of the anatomically defined region that overlapped with significant clusters identified in the TBSS analysis of blast exposure. Not surprisingly, results of an analysis of covariance revealed the blast exposure $\times$ age interaction on mean fractional anisotropy in this region to be highly significant ($P < 0.001$) and also revealed the interaction to be significant ($P < 0.01$) in the other 12 anatomical regions spanning $>500\text{ mm}^3$ in the custom atlas.

Figure 2 Regions throughout cerebral white matter show an interaction between blast exposure and age on diffusion measures. Coronal (A and D), axial (B and E), and sagittal (C and F) slices showing the regions and their overlap where a significant ($P < 0.05$; corrected) blast exposure $\times$ age interaction on diffusion parameters [fractional anisotropy (FA), radial diffusivity (RD), and apparent diffusion coefficient (ADC)] was observed, with blast-exposed individuals exhibiting a more rapid cross-sectional age trajectory towards reduced tissue integrity (dilated from white matter skeleton for visualization). The opposite effect was not seen for any regions. Analyses of the blast exposure $\times$ age interaction on all measures were covaried for gender, education, alcohol use (Lifetime Drinking History score) and PTSD severity (CAPS-IV score). The effect of the interaction on radial diffusivity was widespread and is shown in red, with regions where it overlapped with fractional anisotropy shown in orange and with apparent diffusion coefficient shown in pink (only a few voxels). Regions of overlap for all three measures are shown in yellow. Additionally, there were some regions where the effect was only observed for fractional anisotropy, shown in brown. All regions are overlaid on the FSL-provided (FMRI58) mean fractional anisotropy template in greyscale and associated FMRI58 fractional anisotropy template skeleton, shown in green. Right, anterior, superior convention is used for coordinate reporting.

Dose response to blast

To examine the possibility of a dose response to blast, a median split by number of blasts, with five blasts being the median, was used. Those participants in the blast-exposed group with high blast exposure (five or more blasts, 103 participants) and low blast exposure (less than five blasts, 87 participants) were contrasted for the effect of an interaction with age on diffusion measures at both the voxel and regional levels. A significant interaction was observed in 6 of 36 regions identified in the primary analysis, however there were no significant findings in the voxel-wise analyses ($P > 0.05$; corrected).

Regional mean fractional anisotropy association with ‘years between most severe blast and imaging’

The possibility that accelerated age-associated neurodegenerative effects may be set in motion by exposure to blast

forces can also be visualized in Fig. 4. Colour in this figure is scaled towards green with increasing ‘years between most severe military blast and imaging’ for the 76 participants with close-range blast exposure who had reported substantial information about the details of their worst blast exposure. These participants are also scaled in size to visualize the lifespan trajectory of this subgroup. By age 40, fractional anisotropy for most of those with close-range blast exposure falls below values predicted by their group’s cross-sectional lifespan trajectory. Further support for an effect of YB-blast is presented in Fig. 5, where fractional anisotropy and YB-blast for those with close-range blast are compared in an age- and PTSD severity-matched analysis. This plot shows a significant correlation in the blast-exposed group between fractional anisotropy and YB-blast within the same region as Fig. 4. This analysis was also covaried for the same demographic and clinical variables of the primary TBSS analysis, which included age and CAPS-IV. Significant correlations were not observed in the same region in the blast-unexposed group where the blast-unexposed member’s

Figure 3 The regions exhibiting the blast exposure $\times$ age interaction on fractional anisotropy are within and beyond the boundaries of the regions showing whole-cohort fractional anisotropy association with age. The colour legend applies to both the 2D (A) and 3D (C) models. The region that exhibited significant ($P < 0.05$; corrected) fractional anisotropy association with age in the entire cohort is shown in brown. Heat mapped (2D) and red (3D) regions are those that exhibited both a significant ($P < 0.05$; corrected) difference in their fractional anisotropy association with age between blast-exposed and blast-unexposed groups (blast exposure $\times$ age interaction) and the whole-cohort fractional anisotropy association with age. Shown in yellow are those regions that demonstrated the blast exposure $\times$ age interaction on fractional anisotropy only. The FSL-provided (FMRIB58) mean fractional anisotropy template skeleton is shown in green. In grayscale is the FMRIB58 mean fractional anisotropy template (2D only). Right, anterior, superior convention is used for coordinate reporting. Scatter plot (B) is colour coded with blue and orange features corresponding to blast-exposed and blast-unexposed groups, respectively. Blue circles represent each blast-exposed group participant's data. Orange diamonds represent each blast-unexposed group participant's data. Analysis of mean fractional anisotropy versus age in the region that exhibited significant ($P < 0.05$; corrected) fractional anisotropy association with age in the entire cohort (brown and red regions in 2D and 3D) revealed a more rapid global cross-sectional ageing trajectory towards reduced tissue integrity in the blast-exposed group. Linear (lighter dashed-dotted lines) and quadratic (darker solid lines) models of these trajectories are shown. Dark outlines in either group indicate a TBI by any mechanism (blast-induced or otherwise) during that participant's lifetime. The six participants with moderate or severe TBI in their lifetime were all in the blast-exposed group and are indicated with a black X. Dotted lines show the 95% confidence interval for an observation based on the quadratic models. Fractional anisotropy values are taken from the left hemisphere.

YB-blast values were assigned to that of their age- and CAPS-IV-matched blast-exposed counterpart, suggesting the trajectory is unique to blast-exposed individuals. However, the YB-blast $\times$ age interaction was not

significant. The trend presented in Fig. 5 for the medial orbitofrontal region is representative of what was observed in 5 of 13 regions spanning more than 500 voxels in the custom atlas.

Figure 4 A representative image showing an anatomical region in which the cross-sectional fractional anisotropy age trajectory shows more rapid decline with blast exposure. Colour coding with blue/green and orange corresponds to blast-exposed and unexposed, respectively. Linear (lighter dashed-dotted lines) and quadratic (darker solid lines) models of mean fractional anisotropy versus age in the segment of the left medial orbitofrontal region that overlapped with the significant cluster exhibiting the blast exposure $\times$ age interaction on fractional anisotropy (mean of 671 voxels). Blue circles represent each blast-exposed group participant's data. The subset of participants with close-range blast who were able to report information regarding their blast history sufficient to calculate their YB-blast are increased in size and also scale in colour towards green with increasing YB-blast. Orange diamonds represent each blast-unexposed participant's data. As in Fig. 3, dark outlines in either group indicate a TBI by any mechanism (blast-induced or otherwise) during that participant's lifetime, the participants with moderate or severe TBI in their lifetime ($n = 6$) were all in the blast-exposed group and are indicated with a black X, and dotted lines show the 95% confidence interval for an observation based on the quadratic model. Participants who were either unable to report sufficient blast exposure details to determine their YB-blast or were not exposed to a close-range blast (and thus data were not available) are indicated at zero.

Discussion

The primary finding in this cross-sectional report was that a group of veterans exposed to military-associated blast forces exhibited a significantly more rapid cross-sectional trajectory towards reduced white matter integrity with age compared to a group of veterans without such exposure. Notably, this is in contrast to similar analyses of a TBI $\times$ age interaction where there were no significant findings in the whole cohort or in either group defined by blast exposure; however, such a finding may be more apparent in

a larger, more statistically powered cohort. Military blast exposure may, therefore, be the primary component responsible for negatively deflecting the trajectory of normal age-associated decline in white matter integrity and this effect may be due to neurodegenerative effects, as suggested by the analysis of time since most severe blast. The effect of a dose response to blast at the regional level emphasizes the potential importance of blast exposure in affecting the integrity of white matter over the lifespan. Further, these effects were independent of other clinical comorbidities that affect brain function and structure in this population,

Figure 5 Matched regression analysis of regional mean fractional anisotropy and years between most severe blast exposure and imaging. Fractional anisotropy is plotted versus YB-blast for a subsample of age (± 5 years) and CAPS-IV (± 10 points) matched participants with and without blast-exposure (n pairs = 34) in the same anatomical region of interest segment presented in Fig. 4. In blue/green and orange are the data for blast-exposed and unexposed veterans, respectively. Members of the blast-unexposed group were assigned the value for YB-blast of their blast-exposed age- and CAP-IV-matched counterpart to examine whether the trajectory towards reduced tissue integrity (i.e. fractional anisotropy) with increasing YB-blast was unique to blast exposure. As in Figs 3 and 4, dark outlines in either group indicate a TBI by any mechanism (blast-induced or otherwise) during that participant's lifetime. The three participants in this analysis with moderate or severe TBI in their lifetime were all in the blast-exposed group and are indicated with a black X. Colour mapping identical to that in Fig. 4 (towards green with increasing YB-blast) is applied here to the blast-exposed group for visual comparison with that figure. Dotted lines show the 95% confidence interval for an observation based on the linear model. Age, CAPS-IV score, gender, years of education, and Lifetime Drinking History score were included as covariates in determining significance of the correlation between fractional anisotropy and YB-blast. Asterisk indicates location of two nearly identical data points. NS = not significant.

including PTSD severity. The findings were also independent of participant motion during the DTI acquisition, as the threshold used to exclude participants for excessive motion was conservative compared to what was used by Yendiki *et al.* (2013) in their study specifically investigating the effects of motion on DTI data, and there was no significant group by motion score interaction on fractional anisotropy in any of the regions identified.

Prior work measuring white matter throughout the lifespan finds the volume of white matter increases until reaching a plateau around the fourth decade of life or later, which is likely related to ongoing myelination (Courchesne *et al.*, 2000; Bartzokis, 2001, 2004). This myelination is thought to contribute to a similar trend for fractional anisotropy (Westlye *et al.*, 2010; Lebel *et al.*, 2012). The age at which maximum fractional anisotropy

is reached varies across the brain and also across individuals (Westlye *et al.*, 2010; Lebel *et al.*, 2012). The quadratic model of fractional anisotropy that was used here found that the blast-unexposed group's cross-sectional fractional anisotropy trajectory is consistent with prior studies of normal fractional anisotropy changes across the lifespan (Westlye *et al.*, 2010; Lebel *et al.*, 2012). However, in the blast-exposed group, the trajectory was less arced and more consistently negative. This finding suggests that normal ageing processes may be interrupted, resulting in a negative deflection of the normal trajectory due to blast exposure. Given associations between white matter tissue structure and cognitive and clinical syndromes (Bozzali *et al.*, 2002; Bartzokis, 2004; Bartzokis *et al.*, 2004b, c; Medina *et al.*, 2006; Salat *et al.*, 2006; Kinnunen *et al.*, 2011; Menke *et al.*, 2012), it is possible that individuals with the pathological burden of accelerated white matter ageing could be at higher risk for some of the same cognitive deficits and difficulties with day-to-day life typically associated with these diseases (Gunning-Dixon and Raz, 2000; DeBette and Markus, 2010) at earlier ages. It is currently unclear how blast exposure may influence these developmental trajectories at the individual level and longitudinal follow-up is warranted.

Studies of ageing that report on diffusivity parameters often recruit older participants in age ranges outside of the truncated range recruited by TRACTS, and compare these older individuals to younger adults (Salat *et al.*, 2005a; Bennett *et al.*, 2010; Burzynska *et al.*, 2010). When the current sample of 249 participants was analysed together with TBSS as a single group with no covariates, a substantial portion of the white matter skeleton showed a significant association between fractional anisotropy and age, which is consistent with prior work (Fig. 3A and C). Extracting mean fractional anisotropy values from this entire region for each individual of the cohort revealed similar group-level trajectories as seen at the level of anatomical regions—with the blast-exposed group demonstrating a stronger negative association with age than the group without exposure (Fig. 3B). These data represent a more conservative probe of the blast $\times$ age interaction effects given that regions showing the more substantial age effects are likely to have a more uniform decline across all participants (blast-exposed or not). However, as 76% of the sample was blast-exposed, the strong ageing effect demonstrated in the blast group certainly drives the overall ageing effect and therefore these findings should not be over-interpreted.

When veterans with close-range blast exposure (≤ 10 m) were compared to age- and PTSD symptom severity-matched peers, there was a significant correlation between fractional anisotropy and years since their most severe blast (YB-blast) in some of the same regions that exhibited the blast exposure $\times$ age interaction on fractional anisotropy. Notably, this correlation was not seen in the blast-unexposed group where the blast-unexposed member's YB-blast values were assigned to that of their age- and

CAPS-IV-matched blast-exposed counterpart. This finding of an altered trajectory that was not present in a cohort of similar peers suggests the initiation of detrimental blast-associated processes beyond normal ageing or PTSD-associated neural tissue deterioration. The effect of the interaction between blast exposure and YB-blast on diffusion parameters was not significant ($P > 0.07$; corrected), perhaps due to a reduction in statistical power compared to the primary analysis.

There are limitations to the interpretability of any diffusion-derived parameter as representative of an underlying physiological state or pathology, especially in regions where the parameter's value incorporates data from either tissue or white matter tracts of differing type (partial volume effects) or orientations (crossing fibre effects) (Assaf and Pasternak, 2008). Despite these limitations, a number of studies have demonstrated the utility of DTI for examining the effects of TBI and blast on white matter integrity in both veteran and non-veteran populations (Kraus *et al.*, 2007; Kennedy *et al.*, 2009; Kinnunen *et al.*, 2011, 2012; Davenport *et al.*, 2012; Wada *et al.*, 2012; Bazarian *et al.*, 2013; Morey *et al.*, 2013; Tremblay *et al.*, 2014; Taber *et al.*, 2015). Evidence supporting the utility of DTI to specifically study the effects of blast on white matter integrity is corroborated by a recent study in which Taber *et al.* (2015) report spatially dispersed regions of significantly lower fractional anisotropy in blast-exposed ($n = 29$, 23 with TBI diagnosis) compared with blast-unexposed veterans ($n = 16$). The present data do not replicate the effect they report of a mean fractional anisotropy difference between cohorts, perhaps due to the significant interaction in our cohort, which also spanned a larger age range. It is noteworthy that the average age in their study was 35 years—approximately the age at which one would expect the maximum mean difference in fractional anisotropy in our cohort according to a quadratic ageing trajectory in blast-unexposed individuals. This discrepancy between findings could also be due to unknown differences in the cohorts and merits further study.

The results of this study are cross-sectional and do not demonstrate changes in fractional anisotropy, apparent diffusion coefficient or radial diffusivity in any individual, only that in the given sample of TRACTS participants there is the observation that a group of veterans with blast exposure and a group without exposure show a difference in fractional anisotropy association with age in several regions throughout the cerebral white matter. The hypothesis for a blast exposure $\times$ age interaction on white matter integrity is supported by the significant association between white matter integrity (i.e. fractional anisotropy) and YB-blast in a group of blast-exposed veterans that is absent from a group of age- and PTSD severity-matched YB-blast-adjusted blast-unexposed peers in some of the same regions. These cross-sectional trends will be further investigated as longitudinal data in the TRACTS cohort become available, which include follow-up scans 1–3 years following the baseline, to establish their validity and

potential for detecting accelerated age-associated decline in blast-exposed individuals.

At the cross-sectional level, the white matter integrity of blast-exposed veterans exhibited a stronger negative association with age compared to a group without exposure. Those that do receive the diagnosis of a TBI do not comprehensively represent the population of veterans and service members who may sustain long-term physiological effects often concomitant with blast-induced or other neuro-traumatic injuries. Experiencing a blast alone may be sufficient to interrupt and negatively deflect normal ageing trajectories of white matter integrity. For individuals with a history of blast exposure, the effect of time since blast exposure on white matter integrity could become an important consideration for determining the appropriate course of treatment and predicting clinical outcomes. A follow-up longitudinal study is needed to determine whether the cross-sectional differences in brain ageing trajectories between blast-exposed and blast-unexposed veterans can be observed at the individual level, and whether these structural differences predict differences in clinical outcomes.

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