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White Matter Alterations Are Associated With Cognitive Dysfunction Decades After Moderate-to-Severe Traumatic Brain Injury and/or Posttraumatic Stress Disorder

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ABSTRACT

BACKGROUND: Possible white matter (WM) alterations following moderate-to-severe traumatic brain injury (TBI) and posttraumatic stress disorder (PTSD) and their relationship to clinical outcome have yet to be investigated decades after trauma. We utilized structural magnetic resonance imaging and diffusion tensor images to investigate brain volume and WM alterations in Vietnam War veterans with moderate-to-severe TBI and/or PTSD examined 5 decades after trauma.

METHODS: Data from 160 veterans—history of moderate-to-severe TBI (n = 23), history of TBI+PTSD (n = 36), history of PTSD (n = 53), and control veterans (n = 48)—were obtained from the Department of Defense Alzheimer's Disease Neuroimaging Initiative database. Voxel-based morphometry and tract-based spatial statistics were used to investigate ongoing brain morphometry and WM abnormalities. The fractional anisotropy (FA) and mean diffusivity were then correlated with neuropsychological scores and amyloid deposition in the trauma groups.

RESULTS: Compared with control subjects, the three trauma groups showed gray matter atrophy, lower FA, and distinctly higher diffusivity in the major WM tracts, including the corpus callosum, external and internal capsules, cingulum, and inferior and superior longitudinal fasciculi. The FA and mean diffusivity correlated with cognitive deficits in the trauma groups. Furthermore, the FA in the cingulum correlated negatively with amyloid deposition in the posterior cingulate cortex of all three trauma groups.

CONCLUSIONS: Diffusion tensor imaging detected WM abnormalities that correlated with the severity of present cognitive dysfunction and the degree of cortical amyloid deposition decades after moderate-to-severe TBI and/or PTSD. These results may hint that PTSD secondary to TBI may incur late cognitive sequalae and persistence of brain microstructure alterations.

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Excessive physical force applied to the brain causes traumatic brain injury (TBI) (1), which can lead to long-term behavioral and cognitive deficits, depending on the severity of the TBI. A TBI event also brings an independent risk for posttraumatic stress disorder (PTSD), which is an affective anxiety disorder developing in one third (2) or as many as 50% (3) of TBI survivors in the aftermath of their life-threatening physical trauma. Individuals with TBI and PTSD share similar symptoms of anxiety, depression, and cognitive deficits, which might be associated with persistent structural alterations in brain white matter (WM) and gray matter (GM). Indeed, after TBI, GM atrophy in the prefrontal cortex (PFC) and posterior cingulate cortex (PCC) (4) were observed along with hippocampus volume loss that correlated with the severity of verbal memory deficits and TBI severity (5). Meta-analyses of studies of PTSD survivors indicate a similar scenario of significant GM atrophy in the hippocampus (6), PFC, and anterior cingulate cortex (7,8) compared with findings in demographically matched control subjects.

Extending beyond ordinary indices of GM atrophy, diffusion tensor imaging (DTI) can detect microstructural alterations in WM following trauma. Indeed, this approach has given rise to a considerable literature on DTI changes following TBI, the preponderance of which has focused on observations made in the early months or years after a mild TBI injury. In a review of 100 such articles, Hulkower *et al.* (9) noted that most studies showed reductions in fractional anisotropy (FA) in association with increased mean diffusivity (MD), irrespective of the time passed since the TBI. The few studies of moderate-to-severe TBI have generally shown increased FA and axial diffusivity (AD) at the acute and subacute stages (9,10) versus decreased FA along with increased MD and radial diffusivity (RD) in the first months after TBI (9–11), which were linked with different pathologies, including axonal injuries, neuroinflammation, and

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demyelination (12). In addition, the early changes in the FA values in the cingulum correlated with positron emission tomography (PET) findings of amyloid-β (Aβ) deposition in the PCC (13). Those cross-modal imaging results might imply a relationship between WM damage and Aβ deposition. Indeed, our previous analyses of PET data decades after TBI and/or PTSD revealed increased deposition of Aβ (14) and tau (15) in several cortical regions connected with the cingulum.

In addition, studies of patients with PTSD showed FA changes in both WM and GM regions, including the cingulum, corpus callosum (CC), anterior cingulate cortex, PFC, posterior central gyrus, angular gyrus, and posterior internal capsule (IC) (16,17). The extent of FA reductions in WM correlated with present severity of PTSD symptoms, irrespective of the time passed since the psychologically traumatic event (18,19). Other studies reported increased FA (20,21) or spatially heterogeneous profile of WM alterations, with FA increases or decreases occurring in association with PTSD (22).

In this study, we aimed to address the dearth of literature on the long-term structural and cognitive effects of moderate-to-severe TBI comorbid with PTSD. Therefore, we investigated GM and WM structural alterations in individuals examined decades after experiencing moderate-to-severe TBI and/or PTSD trauma. We also tested for correlations between WM abnormalities with neuropsychological measures and Aβ deposition, in consideration of the reportedly increased risk of Alzheimer's disease among trauma survivors.

METHODS AND MATERIALS

Participant Information

We used data obtained from the U.S. Department of Defense Alzheimer's Disease Neuroimaging Initiative (DOD-ADNI), a nonrandomized neuroimaging study that had recruited Vietnam War veterans to investigate TBI and/or PTSD as potential risk factors for the development of Alzheimer's disease. DOD-ADNI is part of the ADNI project led by Principal Investigator Michael W. Weiner. We were granted approval to use the deidentified data from the ADNI database by the Human Research Ethics Committee of the University of Queensland, Australia (IRB number #2017000630).

A total of 191 individuals had been scanned using structural magnetic resonance imaging and DTI as part of DOD-ADNI. Overall, 13 participants were excluded from our analysis because of changes in the DTI imaging protocol, and 18 participants were excluded because of missing slices (n = 3), massive image (field) distortion (n = 6), or inadequate brain orientation (n = 9). The remaining 160 participants were separated into four cohorts based on the VAELG.csv file provided by the DOD-ADNI administration based on the information provided in (23) into control veterans without service-related injury (n = 48) and TBI (n = 23), TBI+PTSD (n = 36), and PTSD cases (n = 53). The TBI participants had a documented history of moderate-to-severe TBI related to their earlier military services based on the VA/DoD criteria for TBI (24) with a loss of consciousness ≥24 hours, posttraumatic amentia >24 hours, or alteration of consciousness ≥24 hours. The PTSD cases were diagnosed using the DSM-IV and with the criterion of a Clinician-Administered PTSD Scale score >40. In addition, participants with mild cognitive impairment (MCI) had been identified by DOD-ADNI during the recruitment phase based on a clinical dementia rating of 0.5 or more. Self-reported history of injuries to the head or neck either before or after military service was recorded during the screening procedure. In addition to imaging, all participants had participated in neuropsychological assessments by completing several questionnaires described in our earlier publications (14,15).

Magnetic Resonance Image Acquisition

Data acquisition procedures were standardized across all ADNI sites, and study protocol information can be found at https://adni.loni.usc.edu/wp-content/uploads/2017/09/DODADNI_Procedures_Manual_20170912.pdf. In summary, magnetic resonance scans were performed with 3T scanners approved by ADNI. The sequences included 3D T1-weighted anatomical imaging using spoiled gradient echo or magnetization prepared rapid acquisition with gradient-echo with matrix = 256 × 256 × 200 and resolution = 1 × 1 × 1.2 mm. Axial DTI was acquired using axial spin-echo sequence, repetition time/echo time = 9050 ms/minimum, matrix = 256 × 256 × 59, resolution = 1.37 × 1.37 × 2.7 mm^3, and b-value = 5 × b_0 + 41 directions with b = 1000 s/mm^2 (see http://adni.loni.usc.edu/support/experts-knowledge-base/question/?QID=374).

Magnetic Resonance Imaging Data Preprocessing

Data were preprocessed and analyzed using FMRIB's Software Library (FSL 5.0.9) and SPM12 (Statistical Parametric Mapping; www.fil.ion.ucl.ac.uk/spm). All data preprocessing and analyses were conducted blinded to diagnostic grouping. We became unblinded at the stage of the group-level analysis and discussion to make inferences and interpretation of the findings.

T1-weighted images were segmented into GM, WM, and cerebrospinal fluid using the SPM pipeline. Structural data were then spatially normalized using SPM-DARTEL to a study-specific structural template, which generated the normalized T1 images, warp files, and GM deformation maps. These maps were then smoothed with a 10-mm full width at half maximum Gaussian kernel and used as inputs for voxel-based morphometry (VBM) analysis.

DTI data were corrected for eddy current (FSL-eddy correct), and the average of coregistered b_0 volumes was used as a reference. Data were skull stripped using the FSL-bet command and corrected for field bias using N4BiasFieldCorrection from Advanced Normalization Tools (ANTs, version 2.0.1). The FMRIB Diffusion Toolbox Diffusion Toolkit (DFT) was used for the local fitting of the diffusion tensors to generate the FA, MD, AD, and RD maps. Tract-based spatial statistics (TBSS) was used for the voxelwise statistical analysis of the DTI measures, as all the individuals' FA measures were aligned and normalized into the FMRIB58 template-space using FSL-fnirt. The group mean FA images were generated and then skeletonized to identify the centers of all WM tracts in the different study groups with a threshold FA value of 0.2.

Statistical Analysis

To test for differences between the trauma groups in the neuropsychological measures, analysis of variance was used

to compare continuous data and χ^2 test to compare categorical data, both of which were performed in R (version 3.3.1; R Foundation for Statistical Computing, Vienna, Austria) with Bonferroni correction ($p \leq .05$; p.adjust) for multiple comparisons.

Voxel-based analysis for VBM and DTI measures to identify the differences between groups were calculated using the GM deformation maps (for VBM) and DTI measures as inputs for the general linear model with a permutation test. The FA and MD maps were further correlated with the different neuropsychological scores in the three trauma groups. The statistical analysis of the imaging data was performed using FSL-randomise with 1000 permutations and corrected for multiple comparisons using threshold-free cluster enhancement with a familywise error correction ($p \leq .05$). During our statistical analysis, the age, education level, MCI status, ethnicity, and the number of self-reported head and neck injuries were added as confounding variables. In addition, the Aβ [^{18}F]-AV45 PET SUVr values (referenced to the whole cerebellum) derived from the DOD-ADNI Excel file titled UCBERKELEYAV45_20190808.csv were used to calculate the Pearson's correlations between the average of FA in bilateral cingulum and the Aβ deposition in the PCC (corrected with Bonferroni correction [$p \leq .05$]). We chose the PCC region because it is among the first structures to develop Aβ deposition in Alzheimer's disease.

RESULTS

PTSD and TBI+PTSD Groups Show Cognitive Deficits

The demographics of the participants of different groups are presented in Table 1. The TBI+PTSD and PTSD groups showed a greater burden of cognitive deficits than the TBI and control groups, as revealed by higher scores in the everyday cognition test and the American National Adult Reading Test, along with lower scores in the Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MOCA), and Boston Naming Test (BNT) ($p \leq .05$) (Table 2). In addition, there were higher percentages of MCI cases in the TBI (3/23, 13%), PTSD (8/53, 15%), and TBI+PTSD groups (7/36, 19%) compared with the control group (2/48, 4%), but these differences did not attain statistical significance ($p > .23$) (Table 2).

TBI and/or PTSD Might Be Associated With Brain Morphology

The VBM analysis revealed significantly reduced mean total brain volume in the TBI (1132.5 ± 74.8 cm^3, effect size = 0.75, $p = .027$), TBI+PTSD (1035.1 ± 70.5 cm^3, effect size = 1.99, $p = .006$), and PTSD groups (1034.7 ± 92.1 cm^3, effect size = 1.77, $p = .007$) compared with control subjects (1192.6 ± 86.2 cm^3). In contrast to the control group, the GM atrophy in the TBI group was observed in the precuneus, paracentral gyrus, postcentral gyrus, subcallosal gyrus, hippocampus, and thalamus, and relatively modest changes in the right superior parietal gyrus and left precentral gyrus ($p \leq .05$) (Figure 1). Compared with the control group, the TBI+PTSD group exhibited GM atrophy in the left supramarginal gyrus, left middle frontal gyrus, left superior temporal sulcus, right temporal pole, right angular gyrus, right amygdala, right superior occipital gyrus, and bilateral cuneus ($p < .01$). Compared with the control group, the PTSD group showed greater GM atrophy in the superior frontal gyrus, superior and middle occipital gyrus, right hippocampus, right amygdala, supramarginal gyrus, and angular gyrus ($p < .01$).

DTI Revealed Significant Changes in Microstructure Following TBI and/or PTSD

TBSS revealed widespread significant reductions in FA and increases in diffusivity measures in the TBI, TBI+PTSD, and PTSD groups compared with control subjects ($p \leq .05$). Compared with control subjects, the TBI group showed reduced FA values in the external capsule (EC), IC, posterior region of corona radiata, and inferior fronto-occipital fasciculus (IFO) and increased values in the superior longitudinal fasciculus (SLF) (Figure 2A). Compared with the control subjects, the TBI+PTSD group showed reduced FA values in the CC, inferior longitudinal fasciculus (ILF), and EC. The PTSD-alone group showed reduced FA values in the CC, IC, EC, ILF, cingulum, superior region of the IC (SCR), SLF, posterior region of corona radiata, and IFO compared with control subjects (Figure 2A).

Overall, MD was increased in all three trauma groups compared with control subjects. In the TBI group, MD was increased in the cingulum and SLF (Figure 2B). The TBI+PTSD group showed increased MD in the CC, cingulum, SCR, SLF, IC, fornix, ILF, and middle cerebellar peduncle ($p \leq .05$) (Figure 2B). Higher MD values in most of the large WM tracts, including the CC, cingulum, EC, IC, tapetum, anterior commissure, SCR, ILF, SLF, and IFO were seen in the PTSD group (Figure 2B).

Increases in AD and RD in the trauma groups compared with control subjects were present in clusters matching those seen for corresponding MD changes ($p \leq .05$). Thus, the TBI group showed increased AD in the cingulum and SLF (Figure 3A); the TBI+PTSD group showed increased AD in the CC, cingulum, SCR, SLF, IC, ILF, and middle cerebellar peduncle; and the PTSD group showed increased AD in the CC, cingulum, EC, IC, SCR, ILF, SLF, and IFO compared with control subjects (Figure 3A). RD was relatively increased in the TBI, TBI+PTSD, and PTSD groups (Figure 3B).

When comparing the TBI, TBI+PTSD, and PTSD groups with each other, the results showed no differences between the PTSD and TBI+PTSD groups on any of the DTI measures ($p > .05$) and no differences in FA between any of the groups ($p > .05$). However, the TBI+PTSD and PTSD groups showed increased diffusion measures (i.e., MD, RD, and AD) when compared with the TBI group ($p \leq .05$) (Figure 4).

DTI Brain Measures Correlate With Cognitive Status

Overall, there were strong positive correlations of cognitive measures with FA and MD in all three trauma groups ($p \leq .05$). The TBI group showed a positive correlation between the BNT score and the FA map values in the right anterior region of corona radiata and bilateral SLF (Figure S1A); the TBI+PTSD group showed positive correlations in CC, SLF, ILF, IC, EC, tapetum, and IFO (Figure S1A); and the PTSD group showed positive correlations between the BNT scores and FA values in

Table 1. Study Group Demographics and Neuropsychological Assessments of the Study

Demographics	CN	TBI	TBI+PTSD	PTSD	*p*.all	*p*.CN vs. TBI	*p*.CN vs. TBI+PTSD	*p*.CN vs. PTSD
DTI, *n* (% males)	48 (100%)	23 (100%)	36 (100%)	53 (100%)				
Hand, *n* (%)					1	1	1	1
Left	6 (12.5%)	2 (8.70%)	4 (11.1%)	6 (11.3%)				
Right	42 (87.5%)	21 (91.3%)	32 (88.9%)	47 (88.7%)				
Age, Years, Mean (SD)	70.8 (5.59)	68.8 (4.69)	69.1 (3.84)	67.6 (3.05)	.005	.28	.32	.002
Education, Years, Mean (SD)	15.9 (2.16)	15.7 (2.29)	14.8 (2.35)	14.2 (2.10)	.001	.95	.11	.001
Ethnicity, *n* (%)					.874	.92	.93	.92
African American	3 (6.25%)	1 (4.35%)	4 (11.1%)	3 (5.66%)				
American Indian/Alaskan Native	1 (2.08%)	0 (0.00%)	1 (2.78%)	1 (1.89%)				
Asian	3 (6.25%)	0 (0.00%)	0 (0.00%)	0 (0.00%)				
White	39 (81.2%)	20 (87.0%)	29 (80.6%)	45 (84.9%)				
More than one race	1 (2.08%)	2 (8.70%)	1 (2.78%)	3 (5.66%)				
Unknown	1 (2.08%)	0 (0.00%)	1 (2.78%)	1 (1.89%)				
APOE ε4 Status, *n* (%)					.294	1	.39	1
Negative	34 (70.8%)	15 (65.2%)	22 (61.1%)	36 (67.9%)				
Positive	13 (27.1%)	7 (30.4%)	8 (22.2%)	15 (28.3%)				
Unknown	1 (2.08%)	1 (4.35%)	6 (16.7%)	2 (3.77%)				
Head/Neck Self-reported Injury During the War, *n* (%)					<.001	<.001	<.001	.005
None		13 (56.5%)	16 (44.4%)	39 (73.6%)				
Once		9 (39.1%)	17 (47.2%)	13 (24.5%)				
Twice		0 (0.00%)	0 (0.00%)	1 (1.89%)				
Three times		1 (4.35%)	3 (8.33%)	0 (0.00%)				
Head/Neck Self-reported Injury Before the War, *n* (%)					<.001	.001	<.001	.781
None		12 (52.2%)	18 (50.0%)	46 (86.8%)				
Once		7 (30.4%)	14 (38.9%)	6 (11.3%)				
Twice		2 (8.70%)	1 (2.78%)	0 (0.00%)				
Three times		2 (8.70%)	3 (8.33%)	1 (1.89%)				
Head/Neck Self-reported Injury After the War, *n* (%)					<.001	.001	.011	.577
None		12 (52.2%)	26 (72.2%)	46 (86.8%)				
Once	2 (4.17%)	9 (39.1%)	9 (25.0%)	5 (9.43%)				
Twice	0 (0.00%)	0 (0.00%)	1 (2.78%)	0 (0.00%)				
Three times	1 (2.08%)	2 (8.70%)	0 (0.00%)	2 (3.77%)				
MCI Diagnosis, *n* (%)					.26	.52	.23	.49
MCI due to AD	2 (4.17%)	2 (8.70%)	6 (16.7%)	7 (13.2%)				
MCI due to another dementia	0 (0.00%)	1 (4.35%)	1 (2.78%)	1 (1.89%)				
None	46 (95.8%)	20 (87.0%)	29 (80.6%)	45 (84.9%)				
Mother's History of Dementia, *n* (%)					.83	.93	.93	.93
AD dementia	4 (8.33%)	5 (21.7%)	2 (5.56%)	6 (11.3%)				
Non-AD dementia	4 (8.33%)	1 (4.35%)	2 (5.56%)	2 (3.77%)				
No history	2 (4.17%)	1 (4.35%)	2 (5.56%)	3 (5.66%)				
Unknown history	38 (79.2%)	16 (69.6%)	30 (83.3%)	42 (79.2%)				
Father's History of Dementia, *n* (%)					.519	1	.677	.992
AD dementia	1 (2.08%)	1 (4.35%)	4 (11.1%)	2 (3.77%)				
Non-AD dementia	1 (2.08%)	0 (0.00%)	0 (0.00%)	2 (3.77%)				
No history	3 (6.25%)	1 (4.35%)	0 (0.00%)	1 (1.89%)				
Unknown history	43 (89.6%)	21 (91.3%)	32 (88.9%)	48 (90.6%)				

AD, Alzheimer's disease; CN, control veterans without history of combat related TBI or PTSD; DTI, diffusion tensor imaging; MCI, mild cognitive impairment; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury; TBI+PTSD, TBI survivors who developed PTSD following injury.

Table 2. Neuropsychological Assessments in the Study

Neuropsychological Assessments	CN	TBI	TBI+PTSD	PTSD	*p*.CN vs. TBI	*p*.CN vs. TBI+PTSD	*p*.CN vs PTSD	*p*.PTSD vs TBI	*p*.PTSD vs TBI+PTSD	*p*.TBI vs TBI+PTSD
CAPS (Current)	2.60 (4.45)	5.52 (5.81)	39.4 (21.1)	58.0 (13.7)	.84	<.001	<.001	0	<.001	<.001
CAPS (Life)	6.31 (8.89)	13.3 (9.21)	59.7 (21.1)	75.7 (17.4)	.32	<.001	<.001	0	<.001	0
MOCA	24.6 (2.85)	25.1 (3.15)	23.5 (2.86)	23.2 (2.99)	.94	.32	.07	.05	.95	.20
MMSE	28.6 (1.32)	28.7 (1.58)	28.0 (1.70)	27.9 (1.58)	.99	.36	.14	.23	.99	.43
ADAS Total	7.12 (2.88)	6.43 (2.52)	6.81 (2.94)	8.45 (3.03)	.78	.96	.10	.03	.05	.96
ADAS 13	11.2 (4.13)	9.70 (4.02)	11.1 (4.82)	12.9 (4.28)	.49	1.00	.22	.02	.23	.60
CDR (Memory)	0.06 (0.17)	0.13 (0.22)	0.17 (0.27)	0.23 (0.27)	.67	.19	.004	.37	.65	.94
CDR (Global Score)	0.05 (0.16)	0.14 (0.23)	0.14 (0.23)	0.19 (0.30)	.55	.35	.03	.82	.81	1.00
ECog (Memory)	1.54 (0.50)	1.83 (0.64)	2.08 (0.62)	2.23 (0.75)	.29	.001	<.001	.06	.66	.46
ECog (Language)	1.27 (0.35)	1.42 (0.42)	1.64 (0.59)	1.75 (0.51)	.59	.003	<.001	.04	.75	.31
ECog (Visual Spatial)	1.11 (0.19)	1.23 (0.45)	1.35 (0.47)	1.51 (0.60)	.73	.08	<.001	.08	.42	.74
ECog (Plan)	1.08 (0.14)	1.28 (0.37)	1.33 (0.39)	1.45 (0.53)	.21	.02	<.001	.28	.51	.95
ECog (Organize)	1.25 (0.35)	1.72 (0.71)	1.56 (0.66)	1.93 (0.86)	.03	.15	<.001	.63	.06	.80
ECog (Divide Attention)	1.39 (0.53)	1.84 (0.81)	1.88 (0.77)	2.00 (0.84)	.08	.016	<.001	.80	.85	1.00
ECog (Total)	1.09 (0.23)	1.33 (0.41)	1.41 (0.39)	1.55 (0.50)	.09	.002	<.001	.12	.33	.89
CES	13.2 (5.31)	17.2 (7.37)	21.2 (5.35)	21.6 (7.41)	.08	<.001	<.001	.05	1.00	.14
FAQ	0.36 (0.84)	0.78 (1.64)	1.50 (2.56)	1.73 (2.24)	.96	.43	.19	.62	.98	.83
GD Total	0.69 (0.93)	1.52 (1.93)	3.00 (2.46)	4.49 (3.09)	.49	<.001	<.001	<.001	.02	.08
AFQT (Vocabulary)	22.2 (2.50)	21.8 (2.41)	20.8 (4.88)	20.5 (4.86)	.99	.45	.22	.65	.99	.82
AFQT (Object Use)	17.5 (4.09)	18.4 (4.02)	17.9 (4.23)	18.3 (4.05)	.86	.98	.79	1.00	.97	.97
AFQT (Spatial Relation)	14.3 (5.87)	14.4 (5.39)	14.3 (4.76)	13.9 (4.30)	1.00	1.00	.98	.98	.99	1.00
AFQT (Arithmetic Reasoning)	19.1 (3.94)	18.4 (2.73)	17.1 (5.31)	16.4 (5.25)	.96	.28	.04	.38	.91	.76
AFQT (Total Score)	73.6 (12.6)	73.1 (11.5)	69.3 (16.2)	70.3 (12.2)	1.00	.53	.66	.87	.99	.76
AFQT (Percentile Score)	52.7 (25.1)	52.9 (24.0)	48.5 (24.6)	48.2 (22.0)	1.00	.89	.82	.89	1.00	.92
Rey Auditory Verbal Learning Test	12.2 (2.08)	12.9 (2.14)	12.4 (2.31)	12.9 (2.30)	.62	.98	.42	1.00	.75	.85
Clock Drawing Test	4.54 (0.62)	4.83 (0.39)	4.17 (1.06)	4.30 (0.80)	.47	.13	.41	.04	.85	.01
Clock Copy Test	4.77 (0.47)	4.87 (0.34)	4.61 (0.55)	4.72 (0.45)	.84	.42	.94	.56	.72	.17
Category Fluency Test	20.2 (5.33)	21.4 (4.34)	20.0 (6.09)	19.0 (4.39)	.81	1.00	.62	.25	.81	.74
Trail Making Test - Part A	35.6 (13.3)	36.7 (16.5)	38.0 (21.4)	35.8 (11.0)	.99	.89	1.00	1.00	.91	.99
Trail Making Test - Part B	92.8 (47.6)	88.3 (34.3)	112 (59.9)	98.9 (48.6)	.98	.28	.93	.83	.60	.27
Boston Naming Test	28.5 (1.61)	27.8 (1.81)	28.2 (1.91)	27.5 (2.23)	.44	.87	.04	.92	.31	.85
American National Adult Reading Test	13.3 (7.75)	15.5 (8.75)	16.6 (11.1)	19.6 (11.8)	.83	.45	.01	.36	.52	.98

ADAS, Alzheimer's Disease Assessment Scale; AFQT, Armed Forces Qualification Test; CAPS, Clinician-Administered PTSD Scale; CDR, Clinical Dementia Rating; CES, Combat Exposure Scale; CN, control veterans without history of combat related TBI or PTSD; ECog, Everyday Cognitive Test; FAQ, Functional Assessment Questionnaire; GD Total, Geriatric Depression Scale; MOCA, Montreal Cognitive Assessment; MMSE, Mini-Mental State Examination; PTSD, posttraumatic stress disorder; TBI, traumatic brain injury; TBI+PTSD, TBI survivors who developed PTSD following injury.

the bilateral ILF, right SLF, and tapetum (Figure S1A). The TBI group showed a negative correlation of BNT with MD in the IC (Figure S1B); the TBI+PTSD group had negative correlations with MD in the CC, SLF, ILF, SLF, fornix, and corticospinal tract (Figure S1B); and the PTSD group showed a negative correlation with BNT scores in the SLF, arcuate fasciculus, IFO, tapetum, anterior ILF, and IC (Figure S1B).

We found a negative correlation between MOCA scores and FA measures in the posterior CC and SLF of the TBI group (Figure S2), whereas there were positive correlations in the CC, EC, SLF, and ILF in the TBI+PTSD group (Figure S2) and in the SLF and tapetum in the PTSD group (Figure S2). There were no significant correlations between MOCA scores and MD in any group ($p > .05$).

Correlations between MMSE scores and FA in the anterior region of the corona radiata were negative for the TBI group (Figure S3A), while the TBI+PTSD group showed positive correlations in the anterior region of corona radiata, tapetum, SLF, cingulum, IFO, ILF, and IC ($p \leq .05$) (Figure S3A), with no significant correlations in the PTSD-alone group (Figure S3A). A negative correlation was also seen between MMSE scores and MD measures in the anterior region of corona radiata, SLF,

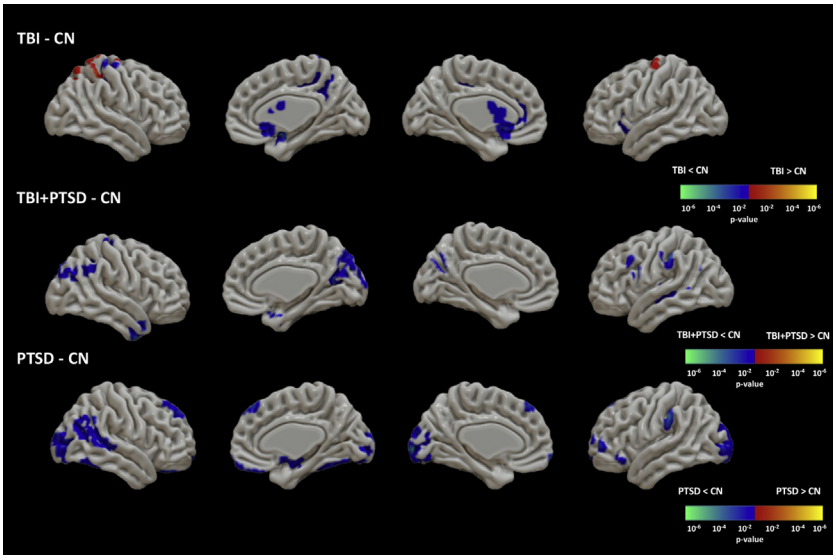

Figure 1. Voxel-based morphometry maps showing the statistical differences (two-sample *t* test) between the three trauma groups as compared with the control Vietnam War veterans, showing volume loss in several brain regions in the veterans with history of traumatic brain injury (TBI) and/or posttraumatic stress disorder (PTSD). All results were corrected for multiple comparisons using familywise error correction with a threshold of $p \leq .05$. Red-yellow represents increased brain volume in the trauma groups compared with control subjects, while blue-green represents decreased brain volume in the trauma groups. CN, control veterans without a history of TBI or PTSD; TBI+PTSD, TBI survivors who developed PTSD following an injury.

ILF, cingulum, and corticospinal tract in the TBI group (Figure S3B); in the CC, tapetum, SLF, cingulum, IFO, ILF, and IC of the TBI+PTSD group (Figure S3B); and in the SLF, ILF, and IFO of the PTSD group (Figure S3B).

DTI Correlates With Aβ Deposition in the Brain

The correlation analysis between [^{18}F]-AV45 PET SUVr in the PCC and FA values in the cingulum revealed a negative correlation in the TBI ($r = -0.66$, $p = .003$), TBI+PTSD ($r = -0.67$, $p < .001$), and PTSD groups ($r = -0.62$, $p = .03$), with no significant correlation in the control group ($r = -0.11$, $p > .05$).

DISCUSSION

This study demonstrated the presence of relative cognitive deficits in the TBI+PTSD and PTSD groups nearly 5 decades following the traumata, which were associated with structural and microstructural abnormalities. Indeed, WM abnormalities in the trauma groups were indicated by increased MD and reduced FA, which further correlated inversely with cognitive status. Moreover, decreased FA in the cingulum showed a negative correlation with Aβ deposition in the PCC, supporting the general finding of long-term negative effects of TBI and/or PTSD on the brain.

Increased Brain Morphology in the Trauma Groups as Compared With Control Subjects May Suggest an Increased Atrophy Following Trauma

Decades following their traumata, both the TBI+PTSD and PTSD groups showed cognitive deficits as compared with the TBI-alone and control groups. In addition, all three trauma groups showed relatively increased morphology in the precuneus, PFC, hippocampus, thalamus, and temporal cortex (Figure 1). The observed pattern of changes in contrast to control subjects was generally consistent with previous literature of TBI showing brain volume loss in the hippocampus (5), thalamus and precuneus (25), and PFC (4) of TBI survivors, and findings that GM volume loss correlates with severity of TBI (4,25). Our findings are also consistent with previous studies reporting reduced hippocampal volume (6,26) and volume loss in the PFC of patients with PTSD (7,8). In patients with PTSD, the hippocampus atrophy was linked to impaired scores in visual-spatial information contextualization (27); the amygdala, insula, and ACC atrophy was linked to impaired processing of emotional salience cues (27,28); and the PFC atrophy was linked to impaired fear learning (27,28). These associations suggest that the observed patterns of brain atrophy in the trauma groups may contribute to the observed relative deficits in neuropsychological measures, i.e., the cognitive deficits seen in the TBI+PTSD and PTSD groups (Table 2). These results should be addressed with caution, as brain atrophy or morphology prior to trauma may also have contributed to the observed differences between the groups. Therefore, longitudinal studies would be required to identify the possible causal relationship between brain atrophy as a result of the trauma.

Microstructural Alterations May Persist in TBI and/or PTSD Decades After Trauma

The TBI group showed minimal WM disruption compared with the TBI+PTSD and PTSD groups, which implies some degree of recovery of WM in the decades after TBI without comorbid PTSD. Indeed, a 3-year longitudinal investigation of survivors with moderate-to-severe TBI showed acutely reduced FA values, followed by pseudo-recovery in subsequent years, where the individual degree of FA normalization correlated with improved cognitive performance (29). This scenario of partial recovery was further supported by the absence of differences in neuropsychological measures between the TBI and control groups in our study. However, PTSD comorbidity with TBI showed extensive clusters of decreased FA and increased diffusivity in the cingulum, CC, IC, and EC, and these findings were associated with relatively poor performance in several neuropsychological tests in the TBI+PTSD group. As such, these results are consistent with the literature reporting WM

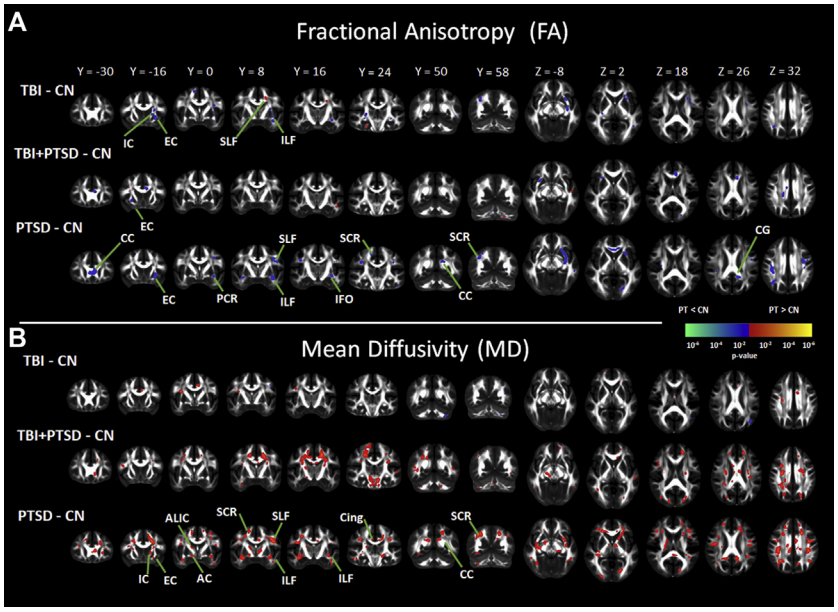

Figure 2. Voxel-based analysis of statistical group differences (two-sample *t* test) in the different diffusion tensor imaging measures. Results show that compared with the control group, **(A)** there was reduced fractional anisotropy (FA) in the traumatic brain injury (TBI) and/or posttraumatic stress disorder (PTSD) groups, along with **(B)** increased mean diffusivity (MD), but mixed increases and decreases in MD in the TBI-alone group. All results were corrected for multiple comparisons using familywise error correction with a threshold of $p \leq .05$. Red-yellow represents increased diffusion tensor imaging parameters (i.e., FA and MD) in the trauma groups as compared with control subjects, while blue-green represents reduced diffusion tensor imaging parameters (i.e., FA and MD). AC, anterior commissure; ALIC, anterior limb of the internal capsule; CC, corpus callosum; CG, cingulate gyrus; Cing, cingulum; CN, control veterans without a history of TBI or PTSD; EC, external capsule; IC, internal capsule; IFO, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; PCR, posterior region of corona radiata; PT, patients; SCR, superior region of internal capsule; SLF, superior longitudinal fasciculus; TBI+PTSD, TBI survivors who developed PTSD following their injury.

changes within a few years following a trauma (29–31), which might suggest that the comorbidity of PTSD with TBI manifests in more extensive and persistent WM alterations in former military personnel, although we cannot infer causality in this cross-sectional study. WM changes after TBI have been linked to neuronal loss (32), neuroinflammation (33), and demyelination (34). Previous animal studies showed demyelination that initiated within a week after TBI and persisted for up to 1 year after TBI (35), a span of time perhaps comparable to several decades of human life. However, the correlations between FA values in the TBI group and both MOCA and MMSE were negative, which seems inconsistent with current literature reports (36,37); resolving this discrepancy will call for further investigations.

Moreover, our results showed that the most widespread alterations observed in the PTSD group were in the CC, superior longitudinal fasciculus, and cingulum bundle, which is consistent with previous findings (16,17,38). However, in any

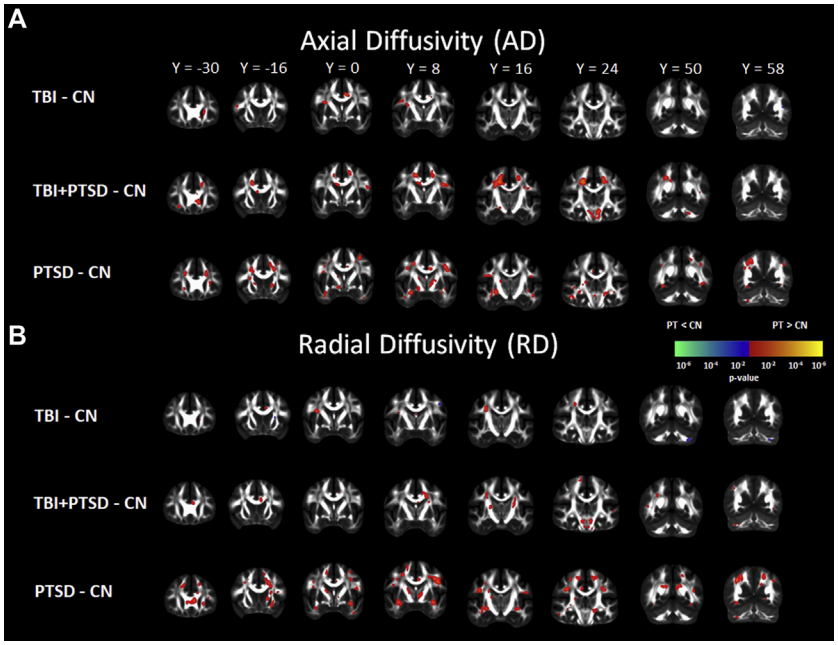

Figure 3. Voxel-based analysis of statistical differences (two-sample *t* test) between the trauma groups in the diffusion tensor imaging diffusivity measures, showing **(A)** increased axial diffusivity (AD) and **(B)** increased radial diffusivity (RD) in all three trauma cohorts (i.e., traumatic brain injury [TBI] and/or posttraumatic stress disorder [PTSD]) compared with the control group. All results were corrected for multiple comparisons using familywise error correction with a threshold of $p \leq .05$. Red-yellow represents greater diffusivity (i.e., RD and AD) in the trauma groups as compared with control subjects, while blue-green represents decreased diffusivity. CN, control veterans without a history of TBI or PTSD; PT, patients; TBI+PTSD, TBI survivors who developed PTSD following their injury.

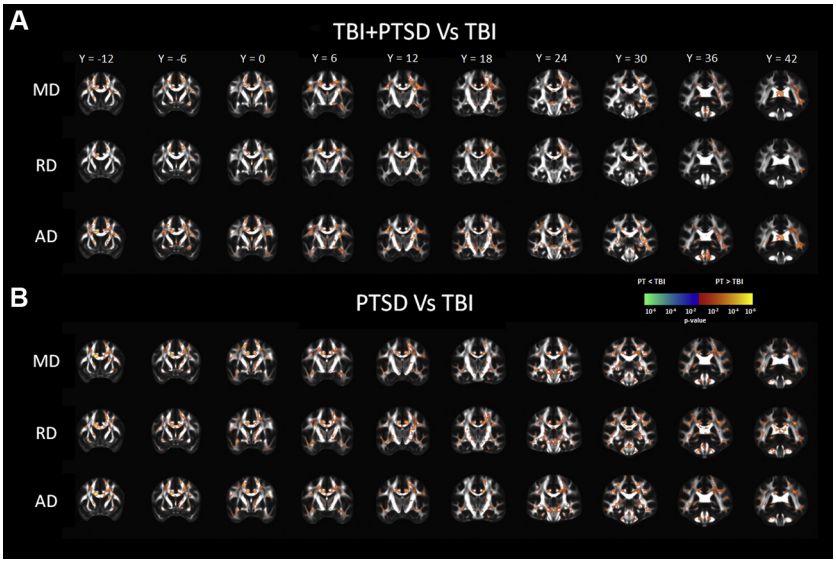

Figure 4. Voxel-based analysis of statistical differences (two-sample *t* test) between the different trauma groups in the diffusion tensor imaging diffusivity measures. The results showed no significant differences in the fractional anisotropy maps in any of the comparisons, either between the traumatic brain injury (TBI) survivors who developed posttraumatic stress disorder (PTSD) following their injury (TBI+PTSD) and TBI groups or between the PTSD and TBI groups ($p > .05$). However, the results showed increased diffusivity measures, including mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD) in **(A)** the TBI+PTSD group as compared with the TBI group and **(B)** the PTSD group as compared with the TBI group ($p \leq .5$). All results were corrected for multiple comparisons using familywise error correction with a threshold of $p \leq .05$. CN, control veterans without a history of TBI or PTSD; PT, patients.

cross-sectional observational study of PTSD, it could be difficult to resolve whether the initial trauma exposure, the genetics of physiological predispositions, or the comorbid psychological effects of PTSD are the main driving factors of late microstructural changes. The nature of the trauma and the age of PTSD onset might importantly influence the degree of observed WM alterations. While this may seem counterintuitive, we note that the spatial pattern of WM alterations in the PTSD-alone group roughly matched that in the TBI+PTSD group, suggesting that PTSD history might be the more decisive factor in the decades-long persistence of microstructural changes after trauma.

The differences in brain structural markers between the TBI and PTSD groups decades after trauma might be related to distinct pathologies such as neuroinflammation (39,40), or to the chronic medications often used to treat PTSD symptoms (41). In addition, the observed increases of the RD index in the PTSD and TBI+PTSD groups may suggest an ongoing demyelination pathology (42). Another study in mild TBI survivors showed similar findings, where PTSD (but not TBI) was independently related to altered microstructure in the caudate region (43).

The WM alterations in the PTSD and TBI+PTSD groups correlated with their current cognitive status. The PGC-ENIGMA PTSD Consortium study in a cohort of 3047 PTSD survivors likewise showed an association between reduced FA in CC with memory deficits (44). This suggests that cognitive difficulties in patients with PTSD may arise from impaired interhemispheric communication of hippocampal and multisensory processing of new information (45) and associative memory function (46). Moreover, negative correlations were observed between the cingulum FA values and Aβ deposition in the PCC in the trauma groups, but not in the control group. Previous work identified the cingulum as the main WM tract connecting the PCC to the PFC (47); hence, its disruption may contribute to the previously observed perturbations in default mode network connectivity reported in TBI (48), PTSD survivors (49), and early Alzheimer's disease (50), implying that DTI might covary with Aβ pathology in cortical regions connected with the same WM tracts. Indeed, Scott *et al.* (13) reported similar findings in TBI survivors, with correlations between increased [^{11}C]-PiB binding in the PCC and reduced FA in the cingulum. We suppose that persistent WM alterations following TBI and/or PTSD may contribute to excess Aβ accumulation or provide a conduit for corticofugal Aβ diffusion (51,52). However, we emphasize that the effect size of elevated Aβ burden in our study groups (14) fell far short of the usual cutoffs for Alzheimer's disease.

While intriguing, this study has a few important limitations. Not least of all, we must be cautious about our interpretation of the findings, given the likely contributions of confounding factors, including drug and alcohol abuse, time since PTSD and TBI onset, comorbid major depressive disorder, hypertension, smoking, body mass index, and stroke. Because of the limited information about these factors in this study, future studies would be required to address the effect of these factors on the ongoing effect of trauma. The severity of the original trauma and the age of PTSD symptom onset add to the difficulty in assessing the time dependence of brain structural alterations in PTSD (38). Furthermore, the temporal order of PTSD onset before or after TBI was unclear in this study, leaving unanswered questions about whether PTSD was secondary to TBI, TBI was secondary to PTSD, or both were occurring at the same time. Participants with self-reported head or neck injury before or after returning to civilian life (Table 1) were not deemed by the DOD-ADNI administration to have met TBI criteria. Future longitudinal prospective studies with extensive neuropsychological documentation might resolve the interplay of causality in the microstructural alterations following TBI and/or PTSD. Furthermore, we concede that the presence of an admixture of MCI-diagnosed cases might have influenced the findings, although we added MCI as

a confounder in the analysis to correct for this heterogeneity. Unavoidably, all participants were male, making it impossible to generalize our findings across gender. An additional limitation lies in the limited directional data of the DTI sequence. More advanced neuroimaging protocols would be helpful in future investigations of TBI and/or PTSD.

Conclusions

To our knowledge, this is the first study to investigate the patterns of WM microstructural changes many decades after moderate-to-severe TBI and/or PTSD in Vietnam War veterans. The spatial extent of the alterations followed a rank order of PTSD > TBI+PTSD > TBI and correlated with relative declines in cognitive status and greater Aβ deposition in the PCC, attesting to the long-term structural damage and cognitive burden experienced by trauma survivors.

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Data used in this article were obtained from the ADNI database (adni.loni.usc.edu). As such, the investigators within the ADNI contributed to the design and implementation of ADNI and/or provided data but did not participate in analysis or writing of this report.

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ARTICLE INFORMATION

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