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Research Article

Traumatic brain injury, posttraumatic stress disorder, and vascular risk are independently associated with white matter aging in Vietnam-Era veterans

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Abstract

Objective: Traumatic brain injury (TBI), mental health conditions (e.g., posttraumatic stress disorder [PTSD]), and vascular comorbidities (e.g., hypertension, diabetes) are highly prevalent in the Veteran population and may exacerbate age-related changes to cerebral white matter (WM). Our study examined (1) relationships between health conditions—TBI history, PTSD, and vascular risk—and cerebral WM micro- and macrostructure, and (2) associations between WM measures and cognition. **Method:** We analyzed diffusion tensor images from 183 older male Veterans (mean age = 69.18; SD = 3.61) with ($n = 95$) and without ($n = 88$) a history of TBI using tractography. Generalized linear models examined associations between health conditions and diffusion metrics. Total WM hyperintensity (WMH) volume was calculated from fluid-attenuated inversion recovery images. Robust regression examined associations between health conditions and WMH volume. Finally, elastic net regularized regression examined associations between WM measures and cognitive performance. **Results:** Veterans with and without TBI did not differ in severity of PTSD or vascular risk (p's >0.05). TBI history, PTSD, and vascular risk were independently associated with poorer WM microstructural organization (p's <0.5, corrected), however the effects of vascular risk were more numerous and widespread. Vascular risk was positively associated with WMH volume ($p = 0.004$, β=0.200, $R^2 = 0.034$). Higher WMH volume predicted poorer processing speed ($R^2 = 0.052$). **Conclusions:** Relative to TBI history and PTSD, vascular risk may be more robustly associated with WM micro- and macrostructure. Furthermore, greater WMH burden is associated with poorer processing speed. Our study supports the importance of vascular health interventions in mitigating negative brain aging outcomes in Veterans.

Keywords: Chronic brain injury; PTSD; vascular diseases; cognitive aging; diffusion tensor imaging; veterans

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Introduction

Given the growing number of Veterans ages 65 and older (Villa et al., 2003), it is crucial to understand the factors that may influence aging outcomes and whether any of those factors increase risk of developing dementia within this population. One factor is traumatic brain injury (TBI), which is prevalent in U.S. military service members (Military Health System, 2023; Raymont et al., 2011). TBI has been identified as a risk factor for dementia (Barnes et al., 2014; Plassman et al., 2000; Snowden et al., 2020), although some work suggests that this is a function of injury severity (Barr, 2020; Dams-O'Connor et al., 2013). To better understand the complex relationship between TBI and dementia, consideration of several risk factors is warranted (Livingston et al., 2020; Veitch et al., 2013). Specifically, Veterans commonly experience a constellation of mental health conditions (e.g., posttraumatic stress disorder [PTSD]) and vascular comorbidities (e.g., hypertension, diabetes) that have also been implicated in pathologic aging (Beristianos et al., 2016; Gottesman et al., 2017; Hinojosa, 2020; Whitmer et al., 2005; Yaffe et al., 2010). While each of these risk factors has been shown to affect the aging trajectory on their own, it remains unclear how mental and vascular health conditions might accelerate aging in individuals with a history of TBI.

While TBI was historically viewed as a singular event with a finite recovery, many now conceptualize TBI as a chronic disease (Dams-O'Connor et al., 2023). The physiological and biochemical processes that occur during TBI can have subsequent, long-lasting effects on the central nervous system (e.g., neuroinflammation, cerebral atrophy) (Sabet et al., 2021). Although the pathophysiology of TBI is not fully understood, previous work suggests that primary injury to the brain causes stretching, shearing, and strain of cerebral white matter (WM). This diffuse axonal injury can

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initiate neurodegenerative cascades that are reflected in decreased WM volumes and impaired communication between brain structures (Greve & Zink, 2009; Narayana, 2017). Normal aging processes also involve deterioration of WM, such as atrophy, disruption of WM tracts, vessel impairments, and demyelination (Liu et al., 2017). Therefore, examining WM may offer insight into the independent and potentially interactive effects of TBI and normal aging on the older adult brain. While it is unknown how a history of TBI affects WM aging, one possibility is that head trauma reduces neurological reserve by altering specific WM tracts, and that damage then interacts with normal aging processes to accelerate brain aging in older TBI survivors. Another possibility is that TBI damages WM tracts in a non-specific manner that results in diffuse damage across a broader array of pathways, which is compounded with increasing age. Studying WM, particularly in aged individuals, could improve our understanding of the effects of TBI on subsequent brain aging processes.

Diffusion tensor imaging (DTI) is a non-invasive magnetic resonance imaging (MRI) technique that characterizes WM by measuring water diffusion along axonal structures. From the images that are acquired, scalar DTI metrics can be generated, including fractional anisotropy (FA, the degree of directionality of water diffusion) and mean diffusivity (MD, which describes the overall water diffusion). Both provide indexes of WM microstructural organization (Chanraud et al., 2010). Recent DTI research suggests that decreases in FA and increases in MD are associated with both normal aging (Bennett & Madden, 2014) and remote TBI (Kraus et al., 2007; Lindsey et al., 2021; Shenton et al., 2012), however, a limited number of studies have focused on older Veterans with remote TBI (Mohamed et al., 2021; Vakhtin et al., 2021). TBI-related alterations in WM organization have also been associated with poorer cognitive performance (Kinnunen et al., 2011; Vakhtin et al., 2021; Yeh et al., 2017), indicating that exacerbated aging of WM following a TBI may be associated with accelerated cognitive decline.

While considerable research has reported the relationship between history of TBI and changes in brain WM, less has focused on an aging Veteran population. Veterans with remote TBI present a unique challenge for understanding the effects of TBI history because they often have additional aging related risk factors such as mental health and vascular conditions. For instance, Veterans with TBI history tend to experience more severe PTSD symptoms than Veterans without (Kaup et al., 2017). Prior work has shown that PTSD is also associated with changes in brain WM, both within the context of TBI and independently (Davenport et al., 2016; Mohamed et al., 2021; Siehl et al., 2018). In addition, both PTSD (Beristianos et al., 2016) and TBI history (Nyam et al., 2019) have been linked to an additional risk factor: greater vascular disease. Vascular disease risk is associated with disrupted white matter organization in older adults (Kennedy & Raz, 2009; Maillard et al., 2015), which is important to consider in this sample given that cerebrovascular dysfunction may be a mechanism by which chronic TBI affects neural organization (Clark et al., 2017; Sullivan, 2019). Vascular health is often overlooked in studies examining the effects of TBI on WM microstructure, and further research on its potentially interactive effects with other health conditions on WM aging is needed. Veterans, particularly older Veterans, offer a unique sample in which we can examine how three risk factors for dementia (i.e., TBI history, PTSD, and vascular conditions) exert individual and cumulative influence on WM microstructure aging, and the extent to which this WM aging may be linked with cognitive outcomes in late-life.

In addition to studying WM microstructural damage, other MRI techniques can be used to quantify and examine WM hyperintensities (WMHs), which are prevalent in an aging population and are thought to reflect macrostructural WM damage within the cerebrum. Growth of existing WMHs has been associated with worsening cognitive performance in older adults (Maillard et al., 2012). Numerous studies suggest that vascular health conditions are associated with greater WMH burden (Dufouil et al., 2001; Moroni et al., 2018), while the literature on WMHs in the context of TBI is more mixed (Berginström et al., 2020; Clark et al., 2016; Lippa et al., 2021), and even less is known about WMHs and PTSD. Ultimately, a study combining information derived from WM micro- and macrostructural alterations may provide unique insights into the mechanisms of TBI history, mental and vascular health, and their interaction with age-related changes to better understand brain and cognitive aging outcomes in at risk populations.

The current study aims to examine the relationships between three risk factors—TBI history, PTSD, vascular risk—and WM micro- and macrostructure (i.e., WMHs), and clarify the extent to which WM is related to cognitive outcomes in a Veteran population. We hypothesize that Veterans who have sustained a TBI will display (1) poorer WM microstructural organization and (2) greater WMH burden. Our examination of the relationship between additional health related variables (PTSD and vascular risk) and WM damage is exploratory. Lastly, we predict that poorer cognitive performance will be associated with lower FA in WM tracts and with greater WMH burden.

Method

Data availability

The present study is a secondary data analysis. Data came from the publicly available Brain Aging in Vietnam War Veterans/Department of Defense Alzheimer's Disease Neuroimaging Initiative (DoD-ADNI) database (adni.loni.usc.edu). This is a multisite longitudinal research study which aims to characterize the long-term effects of TBI and/or PTSD in aging Veterans that involves health assessment, psychiatric interviews, neuropsychological testing, and neuroimaging. Detailed study methods and procedures have been described in previous publications (Weiner et al., 2014), and current information can be found at www.adni-info.org. The DoD-ADNI research was approved by the Institutional Review Boards of all participating sites and completed in accordance with the Helsinki Declaration. Written informed consent was obtained for all study participants. The following study was also approved by The University of Texas at Austin Institutional Review Board and conducted in accordance with the DoD-ADNI Data Use Agreement.

Participants & inclusion/exclusion criteria

The DoD-ADNI study has enrolled 315 Vietnam War Veterans between the ages 50–90. Exclusion criteria for the DoD-ADNI study were as follows: mild cognitive impairment or dementia (Mini-Mental Status Examination score <24 and Clinical Dementia Rating score ≥0.5) at the baseline study visit; history of psychosis or bipolar disorder; alcohol or substance abuse/dependence within the past five years (in accordance with the

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Diagnostic and Statistical Manual of Mental Disorders — Fourth Edition, Text Revision [DSM-IV-TR] (American Psychiatric Association, 2000)); seizure disorder within the past five years; unstable major medical condition (e.g., cancer, HIV infection and AIDS); and clinical evidence of stroke.

The present study sample consisted of 183 male Veterans ages 60–80 (TBI: $n = 95$; Military Control [MC]: $n = 88$) with data available for downloading on 2/20/22. Data for these subjects were excluded from the present analysis for the following reasons: age under 60 or above 80 ($n = 5$); non-male ($n = 1$); TBI within the past 12 months and/or missing head-injury details ($n = 24$); failure to pass neuroimaging quality control standards ($n = 89$); and missing psychiatric data ($n = 13$). Follow-up visit data, if available, was used for Veterans that did not have usable baseline visit data (baseline visit: $n = 167$; 12-month visit: $n = 12$; tau visit: $n = 1$; tau2 visit: $n = 3$). Additional information about study visits can be found in Supplemental Material.

TBI diagnostic assessment

Participants were queried about events for which they may have sustained a head-injury. Self-reported TBI details were used to determine if each reported injury met clinical criteria for TBI and to classify TBI severity, based on the VA/DoD 2016 diagnostic criteria (The Management of Concussion/mTBI Working Group, 2016). An injury was classified as mild if the participant sustained a loss of consciousness (LOC) <30 minutes, alteration of consciousness (AOC) ≤24 hours, or posttraumatic amnesia (PTA) ≤24 hours; or as moderate-to-severe if LOC ≥30 minutes, AOC >24 hours, or PTA >24 hours. MC participants reported no history of LOC, AOC, and PTA, and denied hospitalization due to a previous head-injury.

Psychiatric, vascular, & cognitive assessments

Assessment of PTSD was carried out by the Clinician-Administered PTSD Scale IV (CAPS-IV) (Blake et al., 1995), a structured clinical interview administered during DoD-ADNI screening, resulting in a continuous measure of current posttraumatic stress symptoms in accordance with the DSM-IV-TR (American Psychiatric Association, 2000). Self-reported medical history and physiological measurements were used to characterize cardiovascular health. In accordance with previously utilized metrics of vascular risk burden (Bangen et al., 2014), a vascular burden score (0–5) was calculated based on: (1) hypertension (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, and/or use of antihypertensive medication), (2) endorsement of current diabetes diagnosis, (3) history of cardiovascular disease (i.e., myocardial infarction, cardiac surgery, cardiac failure, and/or angina pectoris), (4) atrial fibrillation, or (5) stroke. Each vascular risk factor was assigned a value of 0 if absent and 1 if present.

Cognitive assessments utilized in this study included Trail Making Test (TMT) Parts A & B, Rey Auditory Verbal Learning Test (RAVLT), and Logical Memory (from the Weschler Memory Scale — Revised; Story "A"). As described in previous work utilizing this dataset (Clark et al., 2021), raw scores were converted to sample-specific z-scores, and domain-specific cognitive composite scores were calculated. The attention/executive functioning composite was created by averaging z-scores from TMT A and B. The verbal learning composite was created by averaging z-scores from the total scores from Logical Memory I and RAVLT Trials 1–5, whereas the verbal memory composite was an average of the Logical Memory II and RAVLT Total Delayed Recall and Recognition trials. Poorer cognitive performance was indicated by higher z-scores on the attention/executive functioning composite, or by lower z-scores on the verbal learning and memory composites.

MRI data acquisition

Data acquisition procedures varied across ADNI sites ($n = 18$) but were based on a standard protocol developed for the ADNI study (https://adni.loni.usc.edu/methods/mri-tool/mri-analysis/). All imaging was performed with 3T scanners (GE: $n = 154$; Siemens: $n = 29$). 3D T1-weighted (T1w) imaging was acquired using spoiled gradient echo or magnetization prepared rapid acquisition with gradient echo with the following range of parameters: TE = 2.9–3.2 ms, TR = 7.0–7.7 or 2300.0 ms, and voxel size = 240 × 156 × 176, 256 × 256 × 192, or 256 × 256 × 196 mm^3. Axial diffusion-weighted imaging (DWI) was acquired using the following range of parameters: TE = 51.8–94.0 ms, TR = 6500.0–14300.0 ms, voxel size = 1.4 × 1.4 × 2.7 or 2.5 × 2.5 × 2.5 mm^3, and $b = 1000$ s/mm^2. Diffusion gradients were applied along either 41 ($n = 154$), 54 ($n = 7$), or 64 ($n = 22$) directions. The 2D fluid-attenuated inversion recovery (FLAIR) sequence was acquired with the following range of parameters: TE = 90.0–156.2 ms, TR = 9000.0–11002.0 ms, and voxel size = 256 × 256 × 35, or 256 × 256 × 42 mm^3.

MRI data processing

White matter microstructure

The neuroimaging analysis pipeline used in this study is depicted in Figure 1, and data processing steps are detailed in the legend. In short, DWI data was preprocessed in FSL (Jenkinson et al., 2012), and probabilistic tractography was conducted using FreeSurfer's TRACULA (TRActs Constrained by UnderLying Anatomy) tool (Maffei et al., 2021; Yendiki et al., 2011). This approach uses estimates of the principal diffusion direction to trace the continuous trajectory of the WM fibers in participant brains and resulted in subject-specific reconstruction of 42 pathways of interest (POIs) along which diffusion metrics (i.e., FA and MD) were extracted at equidistant nodes along the path. Given that tract profiles are generated for each individual across TRACULA's 42 POIs, they are particularly valuable for studying deviation from brain norms in clinical populations (e.g., TBI). Thirty-five POIs that have been previously demonstrated to be vulnerable to age-related changes (Bender et al., 2016; Ziegler et al., 2010) were selected for statistical analysis.

White matter hyperintensity

WMH lesions were segmented using the Lesion Segmentation Tool (LST) in Statistical Parametric Mapping (SPM) (see Figure 1; details provided in legend). The resulting segmentations were restricted to brain WM and used to calculate lesion volumes (in mL).

Statistical analyses

White matter microstructure analysis

Generalized linear model (GLM) analyses were conducted using FreeSurfer's mri_glmfit tool to identify significant associations between FA/MD values along POIs factored by each health condition (i.e., GLMs for 1) TBI history, 2) PTSD, and 3) vascular risk), with follow-up GLMs performed with age and the other health conditions added as covariates (e.g., for TBI history, covariates included age, PTSD, and vascular risk). A cluster-wise threshold of 5% and cluster-forming threshold of 5% with 1000 permutations were used to correct for multiple comparisons, as

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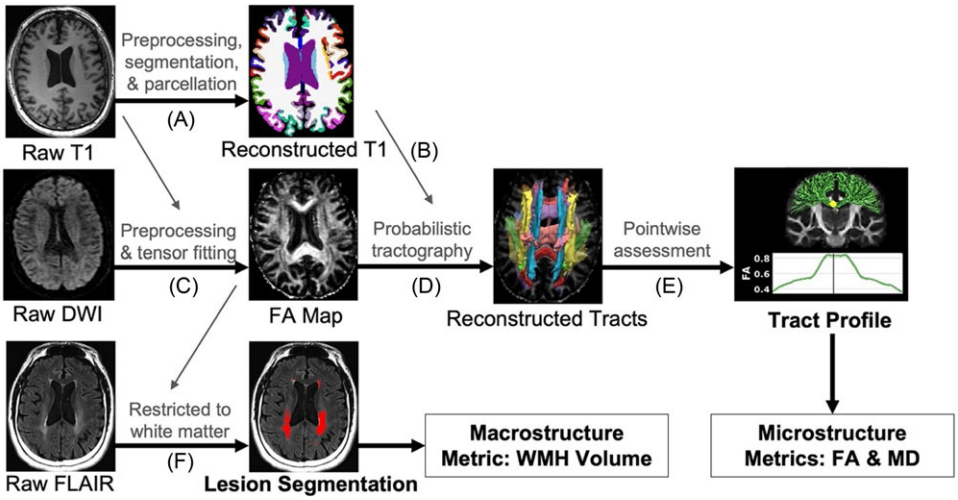

Figure 1. Neuroimaging analysis pipeline. DWI = diffusion weighted imaging; FA = fractional anisotropy; FLAIR = fluid-attenuated inversion recovery; MD = mean diffusivity; PASTA = pointwise assessment of streamline tractography attributes; TRACULA = TRActs constrained by underLying anatomy; WM = white matter; WMH = white matter hyperintensity. The neuroimaging analysis used raw T1-weighted, diffusion-weighted, and FLAIR images to produce metrics of WM micro- and macrostructure. **A)** T1w images were preprocessed, segmented, and parcellated using freeSurfer's recon-all (https://surfer.nmr.mgh.harvard.edu/fswiki/recon-all) and thalamic nuclei segmentation (Iglesias et al., 2018) tools. **B)** The processed T1w image is used to inform the production of tractography streamlines according to a standard atlas. **C)** Because the DWI acquisition did not include reverse phase-encoding or field-maps, the Synb0-disCo (Synthesized b0 for diffusion distortion correction) tool (ver 2.0) was used (Schilling et al., 2020, 2019). This tool applies a network that was trained on the alignment of T1w and $b = 0$ images from an independent dataset to the current study's T1w data to synthesize an "undistorted" $b = 0$ image that is then registered to our raw $b = 0$ image. The two $b = 0$ volumes are concatenated and used as the input to the TOPUP pipeline (Andersson et al., 2003) in FSL (Jenkinson et al., 2012) (ver 6.0) to correct for susceptibility-induced distortions. FSL's BET (Smith, 2002) was then applied to remove nonbrain tissue, and FSL's EDDY tool was used to correct images for eddy currents with the undistorted $b = 0$ volume as a reference. FSL's DTIFIT tool was used for tensor fitting of the preprocessed DWI data to produce FA and MD maps. **D)** Probabilistic tractography was then conducted using the TRACULA (TRActs constrained by underLying anatomy) tool (Maffei et al., 2021; Yendiki et al., 2011) in FreeSurfer (ver 7.3.2). Tract tracing was carried out using FSL's BEDPOSTX algorithm, which applies the ball-and-stick model of diffusion. This resulted in subject-specific reconstruction of 42 pathways of interest (POIs) following the default parameters in TRACULA. **E)** Pointwise assessment of streamline tractography attributes (PASTA) (Jones, Travis, Eden, Pierpaoli, & Basser, 2005) was used to extract diffusion metrics (i.e., FA and MD) at equidistant nodes along the maximum *a posteriori* path. Thirty-five POIs were selected for statistical analysis: anterior commissure; central, parietal, prefrontal, premotor, and temporal bodies of the corpus callosum; genu, rostrum, and splenium of the corpus callosum; and the following bilateral tracts: arcuate fasciculus; anterior thalamic radiations, dorsal and ventral cingulum bundles, corticospinal tract; extreme capsule; fornix; inferior longitudinal fasciculus; middle longitudinal fasciculus; superior longitudinal fasciculi (I, II, and III); and uncinate fasciculus. Tract profile image adapted from https://dmri.mgh.harvard.edu/tract-atlas/. **F)** WMH lesions were segmented using the lesion segmentation tool (LST; ver 3.0)'s lesion prediction algorithm (LPA) (Schmidt, 2017) in statistical parametric mapping (SPM; ver 12). FreeSurfer's SynthStrip (Hoopes, Mora, Dalca, Fischl, & Hoffmann, 2022) was first applied to the FLAIR images to eliminate nonbrain tissue. To restrict the lesion identification algorithm to the brain WM, the FLAIR images were then masked with a WM mask that was generated by thresholding FA maps (produced in the microstructure analysis) at 0.2 and then registering the FA maps to the FLAIR images using FSL's FLIRT. The resulting segmentations were used to calculate lesion volumes (in mL) using the LST.

described in the TRACULA documentation (https://surfer.nmr.mgh.harvard.edu/fswiki/FsTutorial/TraculaStatistics), resulting in a final statistical threshold of $p < .05$, corrected. Two participants were excluded from microstructure analyses due to unresolvable registration errors.

White matter hyperintensity analysis

Robust regression using M-estimation with bisquare weighting (i.e., iterated re-weighted least squares), which reduces the impact of outliers (Venables & Ripley, 2002), was used to examine associations between WMH volume and health conditions (i.e., TBI history, PTSD, and vascular risk), with age as a covariate. Robust regression and 10-fold cross-validation repeated 10 times was conducted in R (ver 4.0.3) using the MASS package (https://github.com/cran/MASS). Due to the non-normal distribution of WMH volumes, raw WMH values were log-transformed for use in statistical analyses. Two participants (previously included in the WM microstructure analysis) were excluded from the WMH analysis due to unresolvable registration errors.

White matter organization & cognitive performance analysis

Elastic net regularized regression with 10-fold cross-validation repeated 10 times was used to identify WM metrics that predicted cognitive performance (i.e., attention/executive functioning, verbal learning, and verbal memory). Elastic net regression was selected because it allows for inclusion of a large number of predictors; the machine learning algorithm weights the proportion of lasso (sum of absolute values of all coefficients) and ridge (sum of squared values of all coefficients) regression penalties to prevent model overfitting. Model predictors included FA/MD values along the tract at each of the nodes found to be significantly associated with health conditions in our WM microstructure analyses, the log-transformed WMH volume, age, and years of education. Variable importance was calculated as the absolute magnitude of the standardized regression coefficient for each predictor. Analyses were conducted using the beset package (https://github.com/jashu/beset) in R. Prior to the generation of cognitive composite scores, outliers (z-scores >3) were winsorized so that raw scores were within three SD of the mean. There were three outliers for TMT Part A, five for TMT Part B, one for RAVLT Trial 1, and one for RAVLT Trial 2. In addition to the four participants missing WM microstructure or WMH data, 18 subjects were excluded from elastic net analyses due to missing cognitive data.

Results

Sample and clinical characteristics

Participant demographics and clinical characteristics are presented in Table 1. Our sample had a mean age of 69.18 years (SD = 3.61 years). The majority of the TBI group endorsed an injury that was

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Table 1. Sample and clinical characteristics

	TBI ($n = 95$)	MC ($n = 88$)
Age [*M* (SD), range]	69.66 (3.55), 61.7–78.9	68.67 (3.62), 61.5–79.1
Sex/Gender [Male; *n* (%)]	95 (100%)	88 (100%)
Ethnicity [*n* (%)]		
Hispanic	5 (5.26%)	10 (11.36%)
Non-Hispanic	88 (92.63%)	78 (88.64%)
Unknown	2 (2.11%)	0 (0.00%)
Race [*n* (%)]		
White	79 (83.16%)	71 (80.68%)
Black	10 (10.53%)	8 (9.09%)
Asian	0 (0.00%)	2 (2.27%)
American Indian or Alaskan Native	1 (1.05%)	1 (1.14%)
Multiracial	4 (4.21%)	4 (4.55%)
Unknown	1 (1.05%)	2 (2.27%)
Years of Education [*M* (SD), range]	15.00 (2.48), 8–20	15.19 (2.30) 12–20
Baseline MMSE Score [*M* (SD), range]	28.16 (1.65), 23–30	28.27 (1.45), 24–30
Baseline CDR Score [*M* (SD), range]	0.17 (0.24), 0–0.5	0.13 (0.22), 0–0.5
TBI History [TBI+; *n* (%)]	95 (100%)	0 (0.00%)
TBI Severity [*n* (% of TBI+)]		
Single mild	20 (21.05%)	—
Multiple mild	9 (9.47%)	—
Moderate/severe	66 (69.47%)	—
TBI Characteristics [n (% of TBI+)]		
LOC	78 (82.11%)	—
AOC	82 (86.32%)	—
PTA	41 (43.16%)	—
Years Since Injury [*M* (SD), range]	40.48 (16.01), 1.1–64.4	—
PTSD [CAPS; *M* (SD), range]	28.44 (23.08), 0–86	28.13 (29.67), 0–92
Vascular Burden [*M* (SD), range, *median*]	1.29 (0.90), 0–3, *1*	1.34 (0.87), 0–3, *1*

AOC = alteration of consciousness; CAPS = Clinician-Administered PTSD Scale; CDR = Clinical Dementia Rating; LOC = loss of consciousness; *M* = mean; MC = military control; MMSE = Mini-Mental Status Examination; PTA = posttraumatic amnesia; PTSD = posttraumatic stress disorder; SD = standard deviation; TBI = traumatic brain injury.
Note: 6 participants (3 TBI, 3 MC) were missing CDR data.

Table 2. TBI history tract profile analysis

FA/MD	Tract	*p*-values	Size (mm^3)	*x*	*y*	*z*
FA	Right corticospinal tract	0.031–0.047	16.9	19.4	−16.9	41.9
FA*	Anterior commissure	0.028–0.042	13.5	34.0	2.2	−29.0
MD	Right superior longitudinal fasciculus II	0.034–0.050	20.3	27.9	−15.8	31.2
MD	Right superior longitudinal fasciculus III	0.005–0.013	23.6	34.2	−9.5	21.9
MD	Splenium of the corpus callosum	0.017–0.029	16.9	10.1	−41.3	11.7

CAPS = Clinician-Administered PTSD Scale; FA = fractional anisotropy; GLMs=generalized linear models; MC = military control; MD = mean diffusivity; TBI = traumatic brain injury.
TBI participants displayed significantly lower FA and higher MD compared to MC participants (* indicates inverse relationship). Corrected p-values represent the lower and upper 90% confidence intervals. Cluster size is represented in mm^3. Location in MNI space was visually approximated as the center of the significant cluster and is represented as *x*, *y*, *z*, coordinates. Tracts remained significant after age, CAPS score, and vascular burden score were included in the GLMs, and these covariate analyses revealed an additional effect of higher MD in TBI participants along the anterior commissure (size = 16.9 mm^3; location = 33.5, 2.9, −29.7; $p = 0.014–0.026$).

determined to be moderate-to-severe in nature (69.47%), and the mean time since most recent injury was 40.48 years (SD = 16.01 years). The sample mean CAPS score was 28.29 (SD = 26.38), and the sample mean vascular burden score was 1.32 (SD = 0.88). The TBI and MC groups did not differ on CAPS or vascular burden scores (p's >0.05). Additional sample and clinical data can be found in Supplemental Material.

White matter microstructure

GLM examination of the POIs revealed that compared to MC participants, TBI participants showed differences in FA and MD along 5 POIs (p's <0.05, corrected; see Table 2), such as lower FA along the right corticospinal tract (see Figure 2). All significant tracts survived covarying for age, PTSD, and vascular risk. Participants with higher PTSD symptomology displayed lower FA along the right uncincate fasciculus (size = 47.2 mm^3; location = 35.0, −5.3, −18.8; $p = 0.000–0.002$), and this association remained significant after covarying for age, TBI history, and vascular risk. Taken together, this suggests that TBI history and PTSD are independently associated with differences in WM organization along multiple POIs.

Associations between vascular risk and FA/MD along POIs were widespread and numerous. GLMs identified significant associations with FA along four tracts and with MD along 28 tracts (p's <0.05, corrected; see Table 3), in which participants with higher vascular risk displayed lower FA and higher MD (e.g., see Figure 3). All significant tracts survived covarying for age, TBI history, and PTSD. These results suggest that higher vascular risk is associated with lower FA and/or higher MD in most of our analyzed POIs.

Several significant interaction effects were identified along POIs between each of the health conditions (i.e., TBI history, PTSD, and vascular risk) and age, as well as between TBI history and PTSD (p's <0.05, corrected). However, post hoc examination of these effects revealed that they are driven by small participant groups

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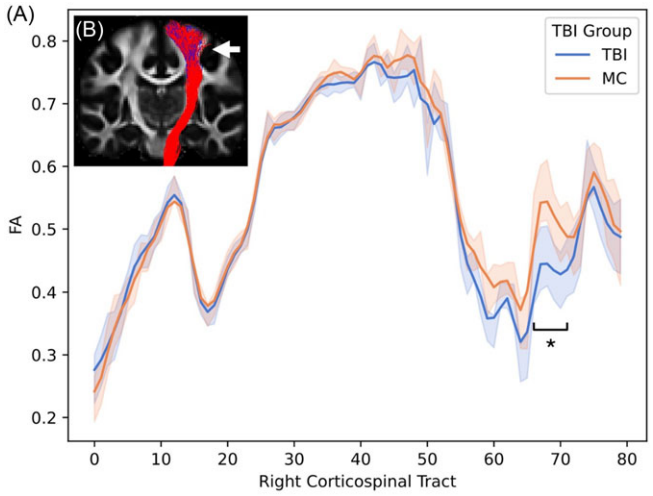

Figure 2. TBI history tract profile plot. FA = fractional anisotropy; MC = military control; TBI = traumatic brain injury. **A)** Compared to MC participants, Veterans with a history of TBI displayed significantly lower FA in a cluster along the right corticospinal tract, indicated by the significance bar (corrected $p = 0.031$–0.047). Shaded regions indicate 95% confidence intervals. **B)** The significant cluster, shown in blue and indicated by the arrow, projected along the right corticospinal tract in FreeSurfer.

(e.g., participants aged >1.5 SD above the mean [$n = 14$]), as the interaction effects were no longer significant once these participants were removed from analysis (see Supplemental Material).

White matter hyperintensity

Robust regression revealed that vascular risk was positively associated with WMH volume ($p = 0.004$, β=0.200, predicted $R^2 = 0.034$), covarying for age, whereas TBI history ($p = 0.202$, β=−0.088) and PTSD ($p = 0.124$, β=−0.024) were not associated with WMH volume (see Figure 4).

White matter organization & cognitive performance

Predicting attention/executive functioning performance using WM microstructure metrics, WMH volume, age, and years of education, the elastic net regression model out-of-sample cross validation predicted $R^2 = 0.052$ (SE = 0.060, Min = 0.026, Max = 0.066). Higher WMH volume was the sole important predictor of poorer attention/executive functioning performance. To examine if this effect is attributable to the attention and/or executive functioning demands of the task, we conducted a post-hoc analysis. A generalized linear model revealed that TMT A ($p = 0.005$), but not TMT B ($p = 0.612$), was significantly associated with WMH volume, covarying for age and years of education. This suggests that the relationship between WMH volume and attention/executive functioning performance as identified by the elastic net regression may be driven by processing speed and motor components captured by TMT A, rather than those specific to set-shifting that may be captured by TMT B.

For verbal learning performance, out-of-sample predictive $R^2 = -0.018$ (SE = 0.013, Min = −0.034, Max = −0.007), indicating that the model added uncertainty to the prediction rather than reducing it. Similarly, out-of-sample predictive $R^2 = -0.026$ (SE = 0.013, Min = −0.044, Max = −0.009) for verbal memory performance. These results suggest that WMH volume, rather than FA/MD in POIs, may be a more robust predictor of poorer attention/executive functioning performance, and that none of the WM metrics may be predictive of verbal learning or verbal memory performance in this sample.

Discussion

Summary

We leveraged publicly available data from a multisite research study of older Veterans to investigate (1) the relationship between TBI history, PTSD, and vascular risk and WM micro- and macrostructure (i.e., WMHs), and (2) associations between these WM measures and cognitive functioning. Overall, our results indicate that (1) vascular health, relative to TBI history and PTSD, may be more robustly associated with WM micro- and macrostructure, and (2) greater WMH burden is associated with poorer processing speed.

White matter microstructure

GLMs revealed associations between FA/MD in clusters along POIs and each of the health conditions (i.e., TBI history, PTSD, and vascular risk). A modest number of clusters were associated with TBI history, independent of the effects of age, PTSD, and vascular risk. These regions of WM generally displayed lower FA and higher MD, which can reflect poorer WM organization (e.g., demyelination, neuronal loss, vasogenic edema). Prior work has shown similar alterations in FA/MD in a select number of WM tracts (Lippa et al., 2023; Mohamed et al., 2021; Morey et al., 2012). One of few military TBI studies to similarly extract diffusion metrics along WM tracts found that middle-aged service members and Veterans with a history of TBI showed similar decreases in FA and increases in MD across multiple WM tracts. Additionally, in Veterans with moderate-to-severe TBI, these microstructure alterations did not resolve at a 2-year follow-up visit (Yeh et al., 2022). Taken together with the results of the present study, in which Veterans are in late adulthood and average 40.5 years since injury, this suggests that TBI-related damage to WM tracts persists into older age and may compound the WM changes associated with normal aging. There is often heterogeneity across studies in the specific tracts associated with TBI, which may be because differences in injury cause (e.g., fall, motor vehicle accident, blast) and injury profile (e.g., coup, contrecoup, acceleration, deceleration) influence the location and degree of axonal shearing and straining. While significant tract clusters identified in the present study presumably represent WM regions in which there is overlapping damage in a meaningful portion of our Veterans, conclusions about the localized effects of TBI are better suited to future studies that may capture more precise injury characteristic data. Interestingly, the tract clusters associated with TBI history in our sample displayed a right lateralization. While some propose right lateralization in age-related decline (Cabeza, 2002; Robertson, 2014), a recent meta-analysis found evidence of left lateralization in the cingulum in TBI (Dennis et al., 2023). Their sample primarily consisted of middle-aged adults with mild TBI, which may account for differences in findings. Our results could indicate that the right hemisphere is more vulnerable to moderate-severe TBI and/or to the long-term effects of TBI damage. Moreover, the discrete number of WM tracts revealed to be associated with TBI seem to support the possibility that TBI reduces neurological reserve in specific WM tracts, which is then compounded by

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Table 3. Vascular risk tract profile analysis

FA/MD	Tract	*p*-values	Size (mm^3)	*x*	*y*	*z*
FA	Left fornix	0.029–0.045	20.2	0.2	−1.7	0.6
FA	Left inferior longitudinal fasciculus	0.004–0.010	33.8	−34.3	−36.8	−3.8
FA	Central body of the corpus callosum	0.002–0.007	33.8	2.5	−16.4	22.8
FA	Temporal body of the corpus callosum	0.014–0.025	27.0	6.7	−34.4	20.2
MD	Left anterior thalamic radiation	0.002–0.008	30.4	−11.7	3.4	3.3
MD	Left arcuate fasciculus	0.030–0.046	20.2	−28.0	8.6	19.5
MD	Left corticospinal tract	0.000–0.002	43.9	−3.3	−26.6	−29.1
MD	Left dorsal cingulum bundle	0.038–0.055	16.9	−6.7	−13.9	28.9
MD	Left extreme capsule	0.014–0.046	37.1	−36.4	−17.0	−13.5
				−31.5	32.1	−5.2
MD	Left inferior longitudinal fasciculus	0.018–0.035	64.2	−34.7	−37.1	−3.6
				−31.0	−49.2	0.9
MD	Left superior longitudinal fasciculus I	0.006–0.014	23.6	−15.9	−39.4	38.2
MD	Left superior longitudinal fasciculus II	0.000–0.002	64.1	−23.1	−4.6	31.4
MD	Left superior longitudinal fasciculus III	0.000–0.004	33.8	−31.6	−15.3	22.1
MD	Left uncinate fasciculus	0.031–0.047	16.9	−15.4	37.3	−6.0
MD	Right anterior thalamic radiation	0.009–0.018	20.2	17.3	7.7	4.1
MD	Right arcuate fasciculus	0.001–0.012	104.7	34.5	22.9	13.7
				30.0	−9.3	24.4
				32.8	−32.1	24.5
MD	Right corticospinal tract	0.002–0.025	40.5	9.3	−25.7	−22.9
				6.7	−29.9	−34.2
MD	Right dorsal cingulum bundle	0.016–0.028	20.2	−6.5	−14.1	28.6
MD	Right fornix	0.037–0.053	27.0	5.3	−15.9	15.4
MD	Right middle longitudinal fasciculus	0.036–0.052	20.2	40.6	−21.3	−1.7
MD	Right superior longitudinal fasciculus I	0.038–0.055	40.4	17.0	−22.6	38.0
				12.4	−47.5	46.6
MD	Right superior longitudinal fasciculus II	0.014–0.025	23.6	27.83	−13.4	31.5
MD	Right superior longitudinal fasciculus III	0.014–0.056	54.0	39.1	−37.2	27.4
				37.4	−31.8	26.5
				35.0	−12.8	22.8
MD	Right uncinate fasciculus	0.014–0.025	20.2	14.6	46.6	−10.8
MD	Central body of the corpus callosum	0.000–0.046	114.7	20.4	−17.3	37.5
				0.5	−16.3	22.7
				−17.9	−18.9	37.3
MD	Parietal body of the corpus callosum	0.002–0.008	101.2	−17.1	−45.4	35.0
				20.3	−43.1	33.7
MD	Prefrontal body of the corpus callosum	0.002–0.021	57.4	−14.7	20.4	21.7
				18.8	21.5	23.0
MD	Premotor body of the corpus callosum	0.001–0.045	64.1	17.2	2.5	35.4
				−14.0	0.9	35.4
MD	Temporal body of the corpus callosum	0.032–0.048	23.6	7.5	−34.8	20.0
MD	Genu of the corpus callosum	0.000–0.002	33.8	−25.9	33.8	7.2
MD	Rostrum of the corpus callosum	0.009–0.019	16.9	−12.6	38.9	−7.6
MD	Splenium of the corpus callosum	0.019–0.031	33.8	3.2	−39.4	10.5
				−20.6	−61.4	16.6

CAPS = Clinician-Administered PTSD Scale; FA = fractional anisotropy; GLMs=generalized linear models; MC = military control; MD = mean diffusivity; TBI = traumatic brain injury.
Higher vascular risk was significantly associated with lower FA and higher MD. Corrected p-values represent the lower and upper 90% confidence intervals. Cluster size is represented in mm^3. For tracts with multiple significant clusters, size was totaled across the clusters. Location in MNI space was visually approximated as the center of the significant cluster and is represented as *x*, *y*, *z* coordinates for each of the significant clusters along the tracts. Tracts remained significant after age, TBI history, and CAPS score were included in the GLMs. These covariance analyses also revealed additional effects such that higher vascular risk was significantly associated with lower FA along the left (size = 20.2 mm^3; location = −33.0, −43.7, 12.8; $p = 0.039–0.057$) and right (size = 27.0 mm^3; location = 35.2, −39.9, 20.0; $p = 0.012-0.022$) arcuate fasciculus, and with higher MD along the anterior commissure (size = 13.5 mm^3; location = −32.0, −3.4, −24.3; $p = 0.041–0.059$) and right extreme capsule (size = 30.4 mm^3; location = 23.9, 16.7, −3.1; $p = 0.000–0.002$).

normal aging processes, as opposed to the possibility that TBI damages WM tracts in a diffuse, non-specific manner.

GLMs also revealed an independent, negative association between current PTSD symptomatology and FA in region along the right uncinate fasciculus, which connects parts of the limbic system to the orbitofrontal cortex. Disrupted organization specifically of the uncinate fasciculus has been associated with PTSD in prior work (Costanzo et al., 2016; Koch et al., 2017) and may be indicative of compromised prefrontal inhibition of the limbic system as implicated in PTSD symptoms such as hyperarousal (Costanzo et al., 2016). In a recent study that also leveraged DoD-ADNI data, tract-based spatial statistics (TBSS) revealed that Veterans with PTSD (defined as CAPS score >40) displayed lower FA across numerous WM tracts compared to Veterans without PTSD (Mohamed et al., 2021). Variability of the WM tracts found to be significant in our studies likely reflect methodological differences in the analysis of this data, however, both patterns of results provide support for the conclusion that PTSD is associated with poorer WM microstructural organization and—importantly—independent of the effects of TBI history.

Of the tract clusters found to be significant in this study, the largest and most widespread effects were those associated with vascular risk. Veterans with higher vascular risk displayed lower FA and higher MD along numerous WM tracts, and these effects were

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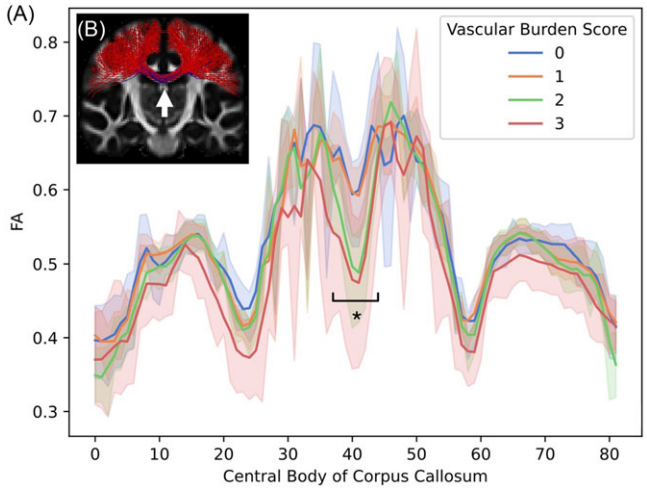

Figure 3. Vascular risk tract profile plot. FA = fractional anisotropy. **A)** Higher vascular risk was significantly associated with lower FA in a cluster along the central body of the corpus callosum, indicated by the significance bar (corrected $p = 0.002–0.007$). Shaded regions indicate 95% confidence intervals. **B)** The significant cluster, shown in blue and indicated by the arrow, projected along the central body of the corpus callosum in FreeSurfer.

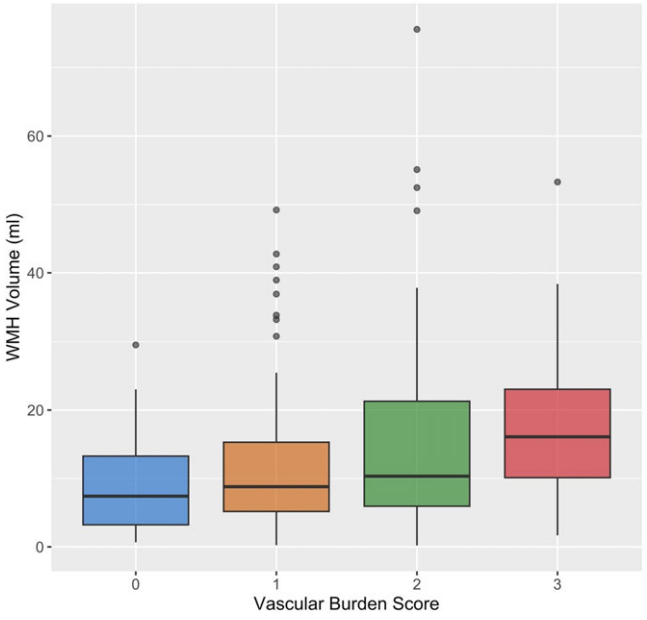

Figure 4. Vascular risk and white matter hyperintensity volume. WMH = white matter hyperintensity. Box plot of vascular burden scores and WMH volumes. The mean WMH volume across all participants was 13.52 mL (SD = 12.33 mL, range = 0.20–75.60 mL). Robust regression revealed that vascular risk was positively associated with WMH volume ($p = 0.004$, β=0.200, predicted $R^2 = 0.034$).

independent of the effects of age, TBI history, and PTSD. Previous work has consistently identified associations between hypertension and disrupted WM organization in both mid-life and late-life (Haight et al., 2018; Power et al., 2017; Rosano et al., 2015), as well as associations between pre-diabetes/diabetes and disrupted WM organization (Hsu et al., 2012; Jing et al., 2022). Both health conditions are thought to induce pathophysiological mechanisms such as endothelial dysfunction, blood-brain barrier dysfunction, neuroinflammation, and oxidative stress (Jing et al., 2022; Li et al., 2023), which may be reflected in alterations to WM microstructure. Hypertension and diabetes were the most prevalent vascular risk factors in the current sample (72.7% and 41.0%, respectively) and, given the relatively low vascular burden scores of the larger sample (mean = 1.32; max = 3), these conditions may represent key drivers of WM aging in this Veteran cohort. Furthermore, the pattern of WM microstructure alterations associated with vascular risk appears unique from that of other examined health conditions (i.e., TBI history and PTSD) such that the majority of our POIs (28/35) displayed higher MD, and a relatively small number of POIs (4/35) displayed lower FA. This is consistent with previous work that found that higher systolic blood pressure was associated with higher MD in all WM regions examined but was not associated with FA in any region. The authors suggest that vascular health conditions such as hypertension may increase blood-brain barrier permeability and lead to accumulation of fluid in extracellular space, as reflected by higher MD, without necessarily damaging the cellular cytoarchitecture, which is thought to be reflected by FA (MacLullich et al., 2009).

In summary, whereas TBI history and PTSD associations were identified in a discrete number of tracts, vascular risk may be implicated in diffuse, non-specific aging of WM microstructure. Although there has been an increased recognition of the importance of accounting for the effects of PTSD when conducting DTI studies of TBI in Veteran populations, vascular health conditions remain rarely considered and offer a crucial domain of further study.

White matter hyperintensity

Robust regression revealed that vascular risk was positively associated with WMH volume, covarying for age, whereas TBI history and PTSD were not associated with WMH volume. The etiology and progression of WMHs is currently understood as heterogenous, although much of the existing literature suggests the pathophysiological mechanisms are vascular in nature (e.g., endothelial dysfunction, microembolization). WM lesions as detected by neuroimaging likely represent regions of demyelination, gliosis, and loss of axons and ependymal cells (Moroni et al., 2018; Rastogi et al., 2021). Numerous studies have identified associations between WMHs and vascular risk factors such as hypertension and diabetes (Dufouil et al., 2001; Li et al., 2023; Murray et al., 2005), which is consistent with the results of the present study. While our finding that TBI was not associated with WMH volume is inconsistent with our hypothesis and with some previous work on remote TBI (Berginström et al., 2020; Riedy et al., 2015), it is in line with work recently conducted by Weiner and colleagues using the DoD-ADNI dataset (Weiner et al., 2023) and aligns with a study that found no association between TBI and WMH volume in Veterans with mild TBI (Clark et al., 2016). Moreover, the findings from our micro- and macrostructural analyses both support the conclusion that vascular risk, relative to remote TBI and PTSD, may be more tightly linked to disruptions in WM organization in older Veterans. Interestingly, a longitudinal study found that lower FA and higher MD in normal-appearing WM at baseline was predictive of WM lesion development 3.5 years later (de Groot et al., 2013). It is possible that alterations to WM microstructure due to vascular health conditions (e.g., hypertension, diabetes), which have been found to occur in mid-life (Haight et al., 2018), may contribute to greater WMH burden in older age.

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White matter organization & cognitive performance

Finally, we wanted to examine whether differences revealed in brain WM were associated with cognitive performance in the older Veteran sample. Elastic net regression identified WMH volume as the sole WM metric predictive of poorer attention/executive functioning performance. However, post-hoc analysis revealed that TMT A was significantly associated with WMH volume, whereas TMT B was not. This finding suggests that WMH volume may be predictive of the gross processing speed and attention components of TMT A and B, rather than the task switching (i.e., executive functioning) component that is exclusive to TMT B. These results are consistent with previous literature relating greater WMH burden to poorer processing speed (Jacobs et al., 2013; Prins & Scheltens, 2015), although they differ from some work suggesting that greater burden is associated with executive dysfunction as well (Jacobs et al., 2013; Li et al., 2023). However, this discrepancy may be due to differences in the severity and extent of WMH damage between the studies. Given that declines in processing speed are a prominent feature of cognitive aging (Albinet et al., 2012; Finkel et al., 2007), it is unsurprising that this was the only domain significantly associated with WM metrics in our sample, which carefully excluded Veterans with MCI or dementia. WM metrics were not predictive of verbal learning or verbal memory performance, which differs from the finding by Clark and colleagues (Clark et al., 2016), who found that deep WMHs were associated with poorer verbal memory performance in relatively young Veterans with a history of mild TBI. This discrepancy could be related to the etiology of the WMHs; in our sample, WMHs were associated with vascular risk and not with TBI history. Contrary to our hypothesis, elastic net regressions revealed that FA/MD in individual clusters along WM tracts found to be significant in our GLMs were not predictive of cognitive performance. Prior work has identified associations between disrupted WM microstructural organization and poorer attention/executive functioning performance in individuals with a history of TBI (Bai et al., 2020; Sorg et al., 2014), however, these studies did not analyze the relationship between WMH burden and cognition. Notably, the value of elastic net regression as used in the present study is its ability to identify the most important predictors. Relative to the localized WM damage identified in clusters along individual POIs, WMH volume appears to be more reflective of widespread WM damage that negatively impacts processing speed.

Strengths & limitations

The present study employed WM tract profile and WMH analyses to identify the independent effects of health conditions on WM aging in a sample of older Veterans decades-removed from injury. However, limitations of the study include: relatively small sample ($n = 183$); limited gender and racial/ethnic diversity (exclusively male; primarily non-Hispanic White); self-report of TBI characteristics (e.g., length of LOC), without Glasgow Coma Scale (GCS) (Teasdale et al., 2014) scores and computerized tomography (CT); lack of performance validity data; self-report of vascular conditions without diagnosis details (e.g., when, by whom), lack of cholesterol data; and exclusion of Veterans with stroke, MCI, or dementia, which may limit conclusions regarding severe vascular disease and dementia risk.

Conclusions

This study leveraged publicly available data to demonstrate that in older Veterans, vascular health is robustly associated with alterations in WM micro- and macrostructure, and poorer WM organization is associated with poorer processing speed. Results highlight that when examining the effects of TBI and/or PTSD on aging, it is crucial to also consider the role of vascular health. This is particularly important in Veterans, who report higher numbers of cardiovascular disease conditions compared to non-Veterans (Hinojosa, 2020). Furthermore, some disparities have been shown in health care access and quality for older Veterans Health Administration users with hypertension and/or diabetes compared to those without (Washington, 2022). Given that vascular health conditions are modifiable risk factors for dementia, addressing such disparities may help mitigate negative cognitive aging outcomes in this vulnerable group. Lastly, our findings highlight the need for further research on the complicated interactions between TBI history, mental health conditions, and vascular comorbidities that may confer increased risk for brain aging.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S1355617724000626.

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