Brain Injury Severity Predicts Longitudinal Change in Perivascular Space Volume in Service Members and Veterans

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Introduction

Traumatic brain injury (TBI) is associated with increased risk of later-life neurodegeneration. Mechanisms linking neurotrauma to chronic brain vulnerability are poorly understood.

- The glymphatic system (GS) utilizes perivascular spaces (PVS) to clear neurotoxic brain waste.[1]
- Enlarged PVS may indicate fluid exchange disruptions that impair brain waste clearance and initiate cell pathology.[2]
- Greater PVS burden is associated with aging, traumatic brain injury, blast exposure, poor sleep, and neurodegenerative disease.[3]

No studies to date have examined how TBI influences long-term longitudinal PVS burden trajectory. This study aimed to associate TBI severity with PVS changes following injury.

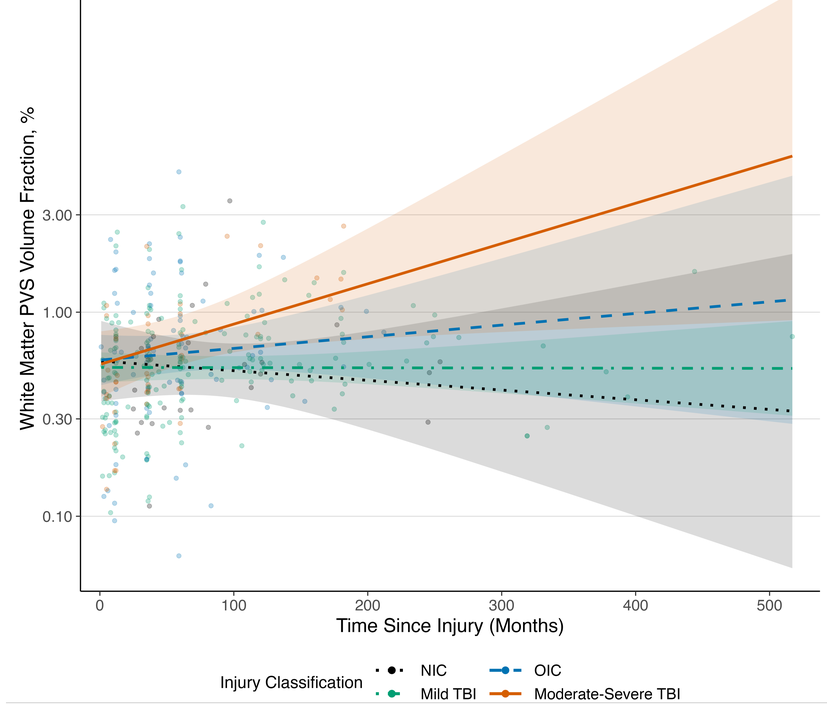
Methods

Participants were 179 unique service members and veterans over 331 scan timepoints enrolled in the Defense and Veterans Brain Injury Center-Traumatic Brain Injury Center of Excellence 15-Year Longitudinal Study with TBI, orthopedic injured controls (OIC), or non-injured controls (NIC). Participants underwent MRI on a 3T scanner at multiple timepoints post-injury (range: 1-517 months). T1- and T2-weighted images were preprocessed and segmented using Freesurfer 7.4. PVS segmentation was performed using the Mapping Vascular and Perivascular spaces (MVP) toolset. PVS burden was quantified as log-transformed white matter (WM) PVS volume divided by WM volume. A mixed effects model was fit to assess the effects of months since injury (TSI), TBI severity category (NIC, OIC, mild TBI, and moderate-severe TBI), age, and TBI number on PVS trajectory, using random intercepts to account for within-subject changes.

Results

The model explained 69.1% of total variance. There was a significant main effect of age (t=6.02; p<.001) with PVS volume fraction increasing at 2.9% per year. There was a significant interaction effect between TSI and TBI severity for the moderate-severe group indicating increasing PVS expansion (7.02% per year) compared to NIC (t=1.99; p=.048). OIC exhibited a trend towards accelerated PVS expansion while mild TBI and NIC demonstrated stable PVS trajectories. Number of TBIs and TSI did not predict PVS change.

Figure: Longitudinal White Matter PVS Trajectories by Injury Group



Characteristic	Non-injured Controls	Orthopedic Injury Controls	Mild TBI	Moderate-Severe TBI	Overall
Participants	18	46	100	15	179
MRI timepoints,	28	81	179	43	331
Participants with ≥2 scans no. (%)	10 (55.6)	24 (52.2)	56 (56.0)	15 (100.0)	105 (58.7)
Age at first MRI, mean (SD)	38.0 (9.8)	38.4 (9.3)	38.7 (10.0)	33.9 (10.2)	38.2 (9.9)
TSI at first MRI, median (IQR), months	57.0 (36.2-105.2)	39.0 (13.0-88.2)	45.5 (9.0-122.0)	7.0 (5.0-65.0)	40.0 (11.5-114.5)
Female sex no (%)	3 (16.7)	3 (6.7)	5 (5.2)	1 (7.1)	12 (6.9)
Total TBIs, median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	1.0 (1.0-2.0)	1.0 (1.0-1.0)	1.0 (0.0-1.0)
WM PVS volume fraction at first MRI, median (IQR)	0.530 (0.337-0.746)	0.625 (0.431-1.093)	0.555 (0.359-0.786)	0.520 (0.391-1.116)	0.566 (0.363-0.890)

Table 1. Demographics

Model Term	β Estimate	95% CI	P Value
A. Fixed Effects			
Time since injury, per month	−.0011	−.0051 to .0030	.60
Age at MRI, per year	.0299	.0201 to .0397	**<.001**
Total Number of TBIs	−.0036	−.1273 to .1201	.95
OIC	.0106	-.4987 to .5198	.967
Mild TBI	-.0725	-.5719 to .4270	.775
Moderate-Severe TBI	-.0384	-.6255 to .5487	.897
TSI × OIC	.0024	−.0026 to .0074	.34
TSI × Mild TBI	.0011	−.0031 to .0052	.61
TSI × Moderate-Severe TBI	.0056	.0001 to .0112	**.048**
B. Model-Estimated Annual Change in PVS Volume Fraction			
NIC	−1.3%	−6.0% to 3.6%	.60
OIC	1.6%	−2.1% to 5.4%	.40
Mild TBI	0.0%	−1.5% to 1.5%	.97
Moderate-Severe TBI	5.6%	0.6% to 10.9%	.028

Table 2. Linear Mixed-Effects Model

Conclusions

- **Moderate to severe TBI may initiate progressive expansion of PVS that persists post-injury and could impair brain waste clearance function in later life.**
- Orthopedic injury and related sequelae (e.g. poor sleep) may also influence PVS trajectory.
- Future research is needed to monitor glymphatic waste clearance mechanisms to mitigate neurodegenerative risk.

Disclaimer: The views expressed in this presentation are those of the authors and do not necessarily reflect the official policy of the Defense Health Agency, Department of War, or the U.S. Government.

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