

Associations between the choroid plexus and age in UK military servicemen and the effects of traumatic brain injury and blast-exposure: an ADVANCE-TBI study

Cheryl RZ See^{1,2}, Grace Blissitt^{1,3}, Lydia Orton^{1,2}, Neil SN Graham^{1,2}, Samantha Paul^{1,3}, Max O Matravers^{1,3}, Sandra L Simpson^{1,3}, Emma Coady^{3,4}, Paul Cullinan⁵, Harriet Kemp⁶, Nicola T Fear^{7,8}, Christopher J Boos^{3,9}, Anthony MJ Bull^{4,10}, Alexander Bennett^{3,4}, David J. Sharp^{1,2}, for the ADVANCE Study

BACKGROUND

The choroid plexus (CP) produces cerebrospinal fluid (CSF) and maintains the blood-CSF barrier. CP volumetric expansion is linked to aging and is thought to reflect a compromised blood-CSF barrier and dysregulated CSF production and clearance. As blast overpressure forces are amplified at tissue-CSF boundaries, the CP and white matter (WM) tissue interfaces at the corpus callosum and lateral ventricle (CC-LV) and middle cerebellar peduncle (MCP)-CSF boundaries may be especially vulnerable. The effects of TBI and blast exposure remains understudied in high-risk military cohorts.

In a military cohort from the ADVANCE study, we hypothesised:

- CP volume increases with age, and this relationship is accelerated by injury exposure.
- TBI severity and blast exposure are associated with compromised CP structure and WM at tissue-CSF interfaces.
- Larger CP volume is associated with poorer clinical outcomes.

We also explored whether blood biomarkers of neurodegeneration collected 3 years prior predicted CP enlargement, and how CP structure relates to overall ventricular structure.

METHODS

- From the ADVANCE cohort: 864 UK soldiers deployed to Afghanistan and Iraq (2003-2014).
- 45% sustained serious combat injury during deployment c.13.7 years prior (the “index” injury).
- 49 healthy controls who did not serve.
- TBI severity ascertained via the Ohio State University TBI Identification Method using Mayo classification for both the Index TBI (combat injury during deployment) and lifetime TBI (worst sustained across the lifetime).
- Clinical outcomes: cognitive assessments (RBANS, D-KEFS, reaction speed) and health-related quality of life (EQ-5D-5L)
- Blood biomarkers of neurodegeneration collected at baseline 3 years prior to the neuroimaging: neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), pTau181, and tau.
- CP structure assessed by volume and mean diffusivity (MD).
- Diffusion metrics (fractional anisotropy (FA) and MD) at the tissue boundaries were derived using the subject-specific diffusion segmentation pipeline (Fig 1).
- Bootstrapped linear regressions with false discovery rate (FDR) correction for multiple comparisons.

SAMPLE CHARACTERISTICS

Table 1. Sample characteristics stratified by index TBI classification.

			Index TBI Classification					
			Controls N = 49	Uninjured N = 476	Injured no TBI N = 170	Symptomatic (possible) N = 61	Mild (probable) N = 119	Moderate severe (definite) N = 38
Age, mean (SD)			37.3 (7.9)	40.5 (5.5)	40.1 (5.8)	39.2 (4.6)	40.4 (5.1)	39.8 (5.7)
Rank, n (%)	Junior	NA	275 (58%)	114 (67%)	46 (75%)	81 (68%)	33 (87%)	
	Senior	NA	130 (27%)	38 (22%)	7 (11%)	27 (23%)	3 (7.9%)	
	Officer	NA	71 (15%)	18 (11%)	8 (13%)	11 (9.2%)	2 (5.3%)	
Ethnicity, n (%)	White	44 (90%)	432 (91%)	150 (88%)	57 (93%)	108 (91%)	32 (84%)	
Amputee Status, n (%)			0 (0%)	1 (0.2%)	33 (19%)	23 (38%)	36 (30%)	17 (45%)
Blast Exposure, n (%)			0 (0%)	247 (52%)	137 (81%)	57 (93%)	111 (93%)	34 (89%)

Figure 1. Image processing workflow for the subject-specific diffusion segmentation pipeline.

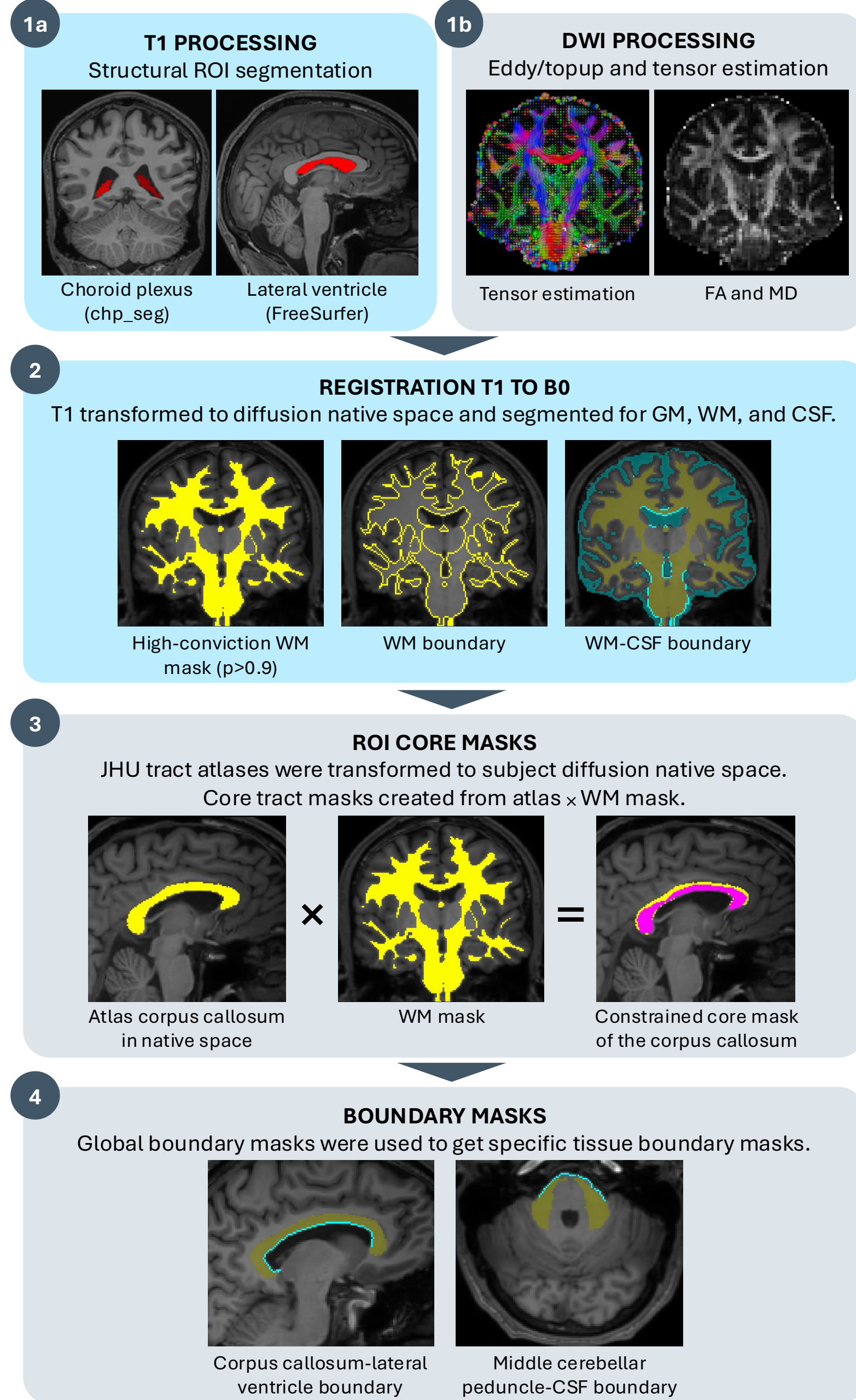
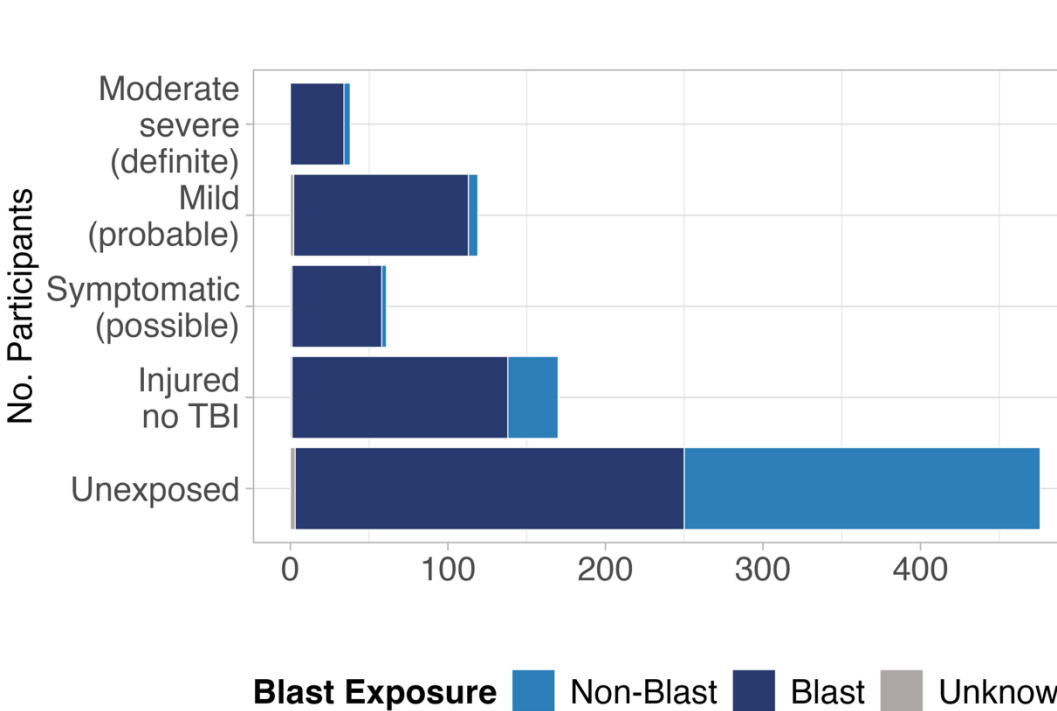


Figure 2. Blast exposure by index TBI classification.

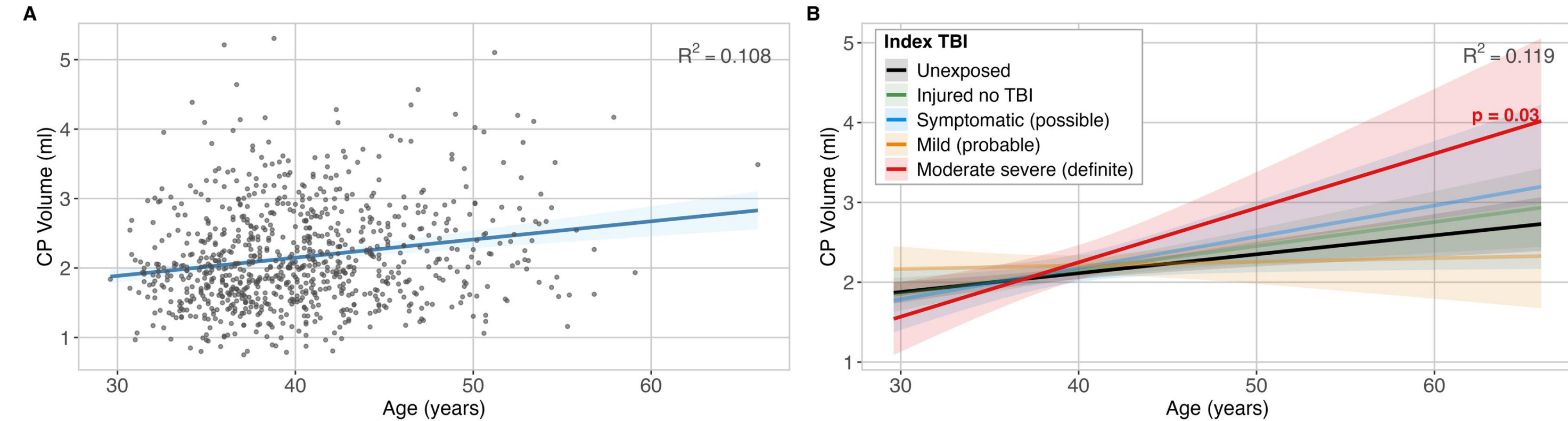


RESULTS

CP VOLUME INCREASED WITH AGE, WITH TBI POTENTIALLY AFFECTING THIS RELATIONSHIP

CP volume increased with age ($B = 0.026$, $p_{FDR} < 0.001$; Fig. 3A). Participants with a moderate-severe index TBI had a steeper association between CP volume and age compared to uninjured soldiers, but this did not survive FDR correction ($p = 0.03$, $p_{FDR} = 0.09$; Fig 3B).

Figure 3. (A) Choroid plexus volume increases with age; (B) this relationship may be affected by moderate-severe combat TBI exposure.



NEITHER TBI NOR BLAST EXPOSURE COMPROMISED CP STRUCTURE OR THE WM-CSF BOUNDARY

There were no group differences across TBI severity or blast exposure in: (a) CP volume or MD; or (b) the mean FA and MD at the tissue boundaries of the CC-LV and MCP-CSF (all $p_{FDR} > 0.05$).

CP VOLUME WAS UNRELATED TO COGNITION AND QUALITY OF LIFE

CP volume was not associated across all cognitive domains tested (RBANS, D-KEFS, reaction speed) nor EQ-5D-5L (all $p > 0.05$).

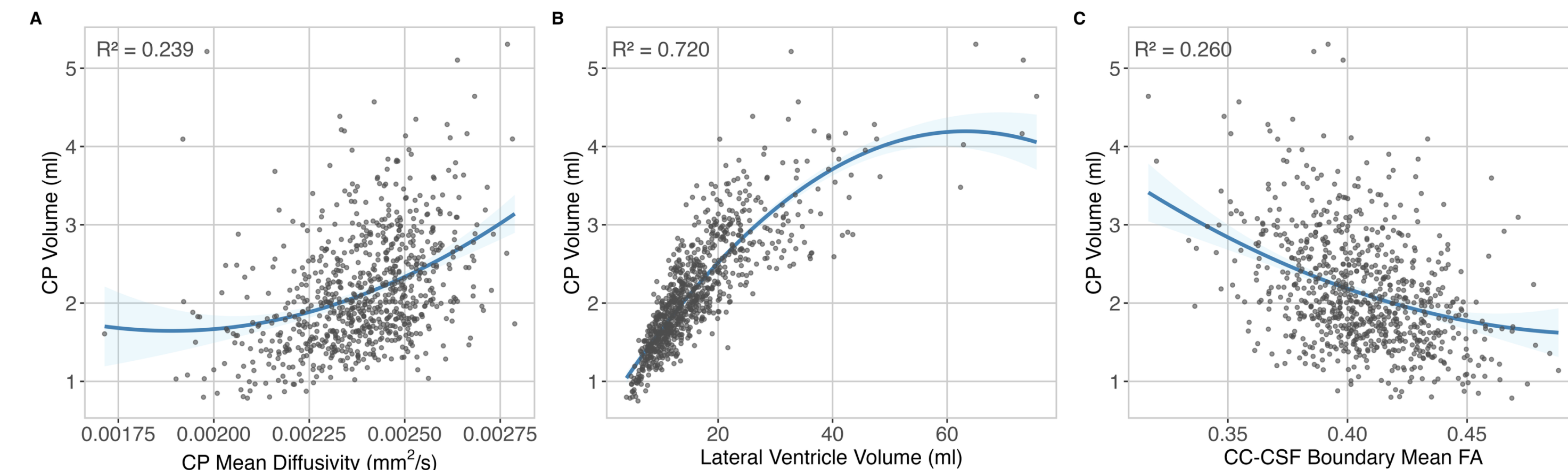
HIGHER LEVELS OF GFAP FROM 3 YEARS PRIOR PREDICTED LARGER CP VOLUMES

CP volume increased with $\log_2$ GFAP levels, but this did not survive correction for multiple comparisons ($B = 0.097$, $p = 0.03$, $p_{FDR} = 0.11$; Fig. 4). NfL, pTau181, and tau were not associated with CP volume (all $p_{FDR} > 0.05$).

CP VOLUME RELATES TO VENTRICULAR STRUCTURE

Greater CP volume had a non-linear association with higher CP MD values indicating larger volumes may relate to compromised microstructure ($p_{FDR} < 0.001$; Fig 5A). Greater CP volume also exhibited a non-linear relationship with larger lateral ventricle volumes ($p_{FDR} < 0.001$; Fig 5B) and lower FA of the WM at the CC-LV boundary ($p_{FDR} = 0.02$; Fig 5C).

Figure 5. The relationship between CP volume and measures of ventricular structure: (A) CP mean MD; (B) lateral ventricle volume; and (C) mean FA of the WM at the CC-LV boundary.



CONCLUSIONS

CP volume increased with age, where this relationship was potentially worsened by moderate-severe combat TBI but not blast exposure. Over a decade post-injury, WM-CSF boundary microstructure and CP structure were unrelated to TBI or blast exposure. Larger CP volumes were associated with higher MD, greater LV volume, and reduced FA at the CC-LV boundary suggesting CP enlargement could reflect compromised tissue integrity, and could relate to ventricular expansion straining neighbouring WM tracts via dysregulated CSF production/clearance.

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