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Background

- Background:** Repetitive head impacts (RHI) from American football are associated with long-term alterations in white matter (WM) microstructure. Prior research suggests that younger age of first exposure (AFE) to football increases vulnerability to white matter (WM) pathology later in life, but the interplay among AFE, WM microstructure, and clinical outcomes remains unclear.
- Aim:** This study investigates the association between AFE to RHI in former football players and long-term alterations in CC white matter microstructure using diffusion tensor imaging (DTI).

Methods

- 172 former football players from the DIAGNOSE-CTE Research Project underwent diffusion weighted MRI and neuropsychological testing (**Table 1**).
- Tests examining memory and executive function were a priori selected (Trails A&B, Neuropsychological Assessment Battery List Learning Immediate and Delayed Recall, and the Brief Visuospatial Memory Test Immediate and Delayed Recall).
- DTI metrics, including fractional anisotropy (FA) and mean diffusivity (MD), were quantified in corpus callosum (CC) subregions (genu, body, splenium) using the Generalized Tract Based Spatial Statistics Pipeline.
- Linear regression models examined associations between AFE and DTI metrics, adjusting for age, MRI site, education, and total years of football.
- Additional models evaluated associations with cognition and tested AFE×DTI metrics interaction effects.

Table 1. Demographics

	N	Football Players
Age (years)	172	57.33 (8.29)
Education (years)	172	16.74 (1.47)
History of Learning Disability (y/n)	169	18 (11%)
Race	172	
Black or African-American		59 (34%)
White		110 (64%)
Multiple races selected		3 (1.7%)
Total years of play	172	15.81 (4.39)
Age of first exposure	172	11.14 (2.84)
TES Level of CTE Certainty	171	
No TES		61 (36%)
Suggestive of CTE		32 (19%)
Possible CTE		21 (12%)
Probable CTE		57 (33%)
Revised Framingham Stroke Risk Profile	163	0.032 (0.034)
APOE e4 Carrier	166	49 (30%)

Mean (SD); n (%)

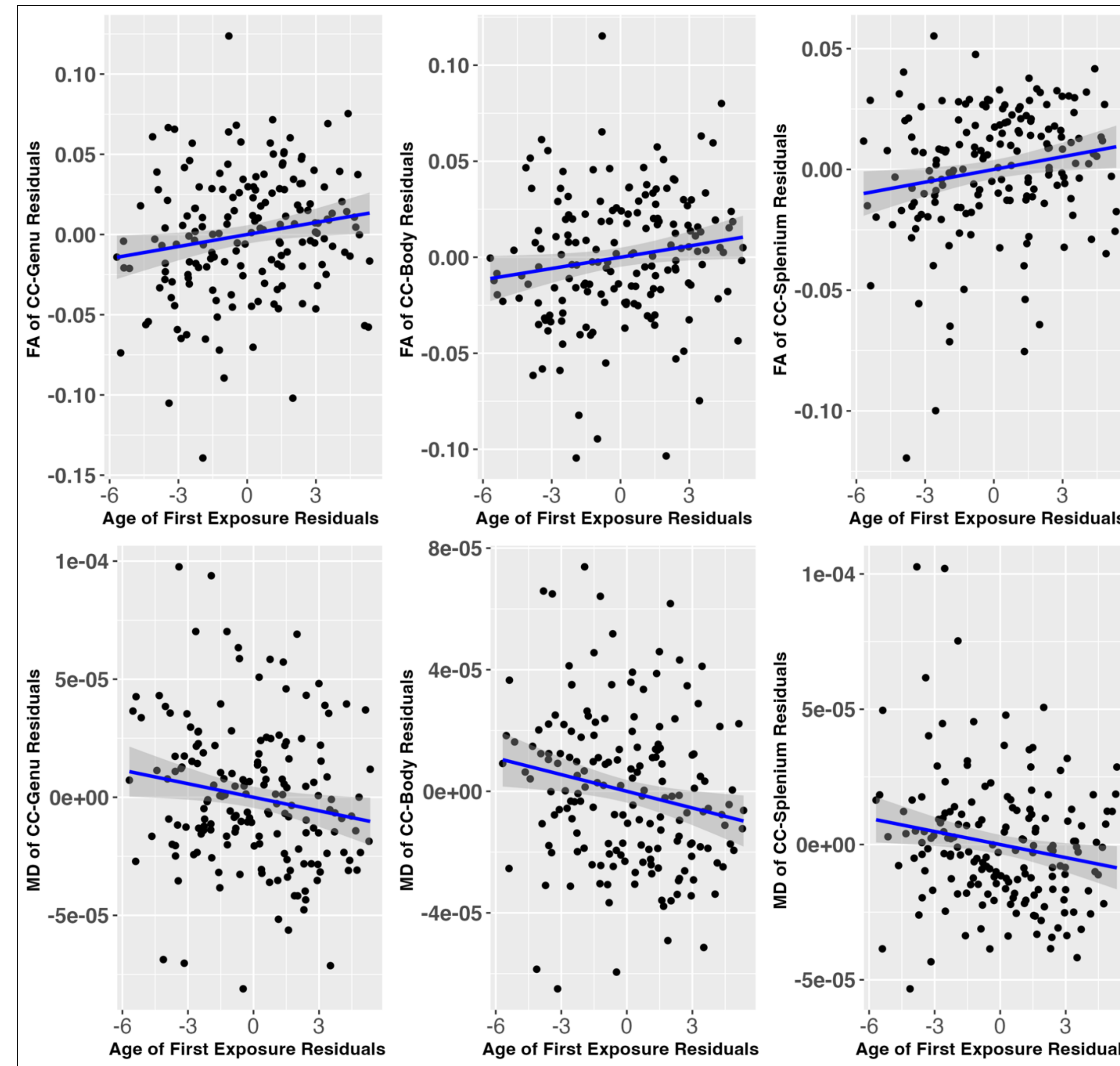


Figure 1. Partial regression plots show associations between AFE and FA/MD in corpus callosum (CC), adjusted for age, total years of football, and site. Earlier age of first exposure was associated with lower FA and increased MD across corpus callosum regions.

Results

- Younger AFE was associated with lower FA and higher MD across corpus callosum regions.
- Significant associations were observed for FA in the genu (Unstd.β=2.5×10⁻³, p=0.025), body (Unstd.β=1.95×10⁻³, p=0.044), and splenium (Unstd.β=1.76×10⁻³, p=0.021), and for MD in the genu (Unstd.β=-1.91×10⁻⁶, p=0.029), body (Unstd.β=-1.83×10⁻⁶, p=0.012), and splenium (Unstd.β=-1.61×10⁻⁶, p=0.021). (**Figure 1**)
- AFE was not directly associated with cognitive test performance.
- Interaction models revealed AFE moderated the relationship between DTI metrics and cognition; lower FA and higher MD were associated with disproportionately worse cognitive scores among individuals with earlier exposure, whereas cognitive scores among later-exposed individuals were relatively insensitive to WM microstructure (**Table 2**).

Conclusions

- Younger AFE to football was associated with microstructural alteration in the CC that are aligned with more WM degeneration.
- AFE moderated the relationship between WM microstructure and cognitive performance, with greater vulnerability to WM alterations among those exposed earlier.
- These findings suggest that earlier exposure to RHI may lead to an increased vulnerability to long-term neuropathological consequences in the white matter.

Table 2. Results

	FA: CC Genu				FA: CC Body				FA: CC Splenium			
	B (95% CI)	t	p-value		B (95% CI)	t	p-value		B (95% CI)	t	p-value	
Trails A	9.02 (-8.17, 26.20)	1.04	0.302		14.09 (-7.71, 35.90)	1.28	0.204		7.57 (-18.36, 33.51)	0.58	0.565	
Trails B	59.45 (-1.34, 120.24)	1.93	0.055		94.06 (16.87, 171.26)	2.41	0.017		55.11 (-38.47, 148.70)	1.16	0.247	
NAB Immediate	-5.52 (-11.70, 0.65)	-1.77	0.079		-8.07 (-15.96, -0.19)	-2.02	0.045		-10.94 (-20.13, -1.75)	-2.35	0.020	
NAB Long Delay	-3.83 (-7.77, 0.11)	-1.92	0.056		-5.24 (-10.29, -0.20)	-2.05	0.042		-3.73 (-9.67, 2.21)	-1.24	0.217	
BVMT Immed.	-9.30 (-18.33, -0.27)	-2.03	0.044		-13.90 (-25.39, -2.42)	-2.39	0.018		-5.71 (-19.56, 8.14)	-0.81	0.417	
BVMT Long Delay	-3.66 (-7.30, -0.02)	-1.98	0.049		-5.83 (-10.44, -1.23)	-2.5	0.013		-3.03 (-8.60, 2.53)	-1.08	0.283	
	MD: CC Genu				MD: CC Body				MD: CC Splenium			
	B (95% CI)	t	p-value		B (95% CI)	t	p-value		B (95% CI)	t	p-value	
Trails A	-2.39×10 ⁴ (-4.46×10 ⁴ , -3.28×10 ³)	-2.29	0.023		-1.79×10 ⁴ (-4.35×10 ⁴ , 7.75×10 ³)	-1.38	0.17		-1.19×10 ⁴ (-3.76×10 ⁴ , 1.37×10 ⁴)	-0.92	0.360	
Trails B	-8.85×10 ⁴ (-1.63×10 ⁵ , -1.37×10 ⁴)	-2.34	0.021		-8.35×10 ⁴ (-1.76×10 ⁵ , 8.82×10 ³)	-1.79	0.076		-5.50×10 ⁴ (-1.48×10 ⁵ , 3.78×10 ⁴)	-1.17	0.244	
NAB Immediate	9.19×10 ³ (1.74×10 ³ , 1.66×10 ⁴)	2.44	0.016		9.71×10 ³ (5.45×10 ² , 1.89×10 ⁴)	2.09	0.038		9.21×10 ³ (1.18×10 ¹ , 1.84×10 ⁴)	1.98	0.050	
NAB Long Delay	6.56×10 ³ (1.81×10 ³ , 1.13×10 ⁴)	2.73	0.007		6.82×10 ³ (9.70×10 ² , 1.27×10 ⁴)	2.3	0.023		6.10×10 ³ (2.02×10 ² , 1.20×10 ⁴)	2.04	0.043	
BVMT Immed.	1.00×10 ⁴ (-1.06×10 ³ , 2.11×10 ⁴)	1.79	0.076		1.09×10 ⁴ (-2.74×10 ³ , 2.45×10 ⁴)	1.58	0.117		9.38×10 ³ (-4.07×10 ³ , 2.28×10 ⁴)	1.38	0.171	
BVMT Long Delay	4.03×10 ³ (-4.16×10 ² , 8.47×10 ³)	1.79	0.075		4.46×10 ³ (-9.89×10 ² , 9.91×10 ³)	1.62	0.108		4.00×10 ³ (-1.38×10 ³ , 9.38×10 ³)	1.47	0.144	

AFE significantly moderated the relationship between WM microstructure and cognition. Lower FA and higher MD were associated with disproportionately worse cognitive performance among individuals with earlier exposure, whereas performance among later-exposed individuals was relatively insensitive to variation in WM microstructure. All estimates are adjusted for covariates including age, site, total years of football play, and education.