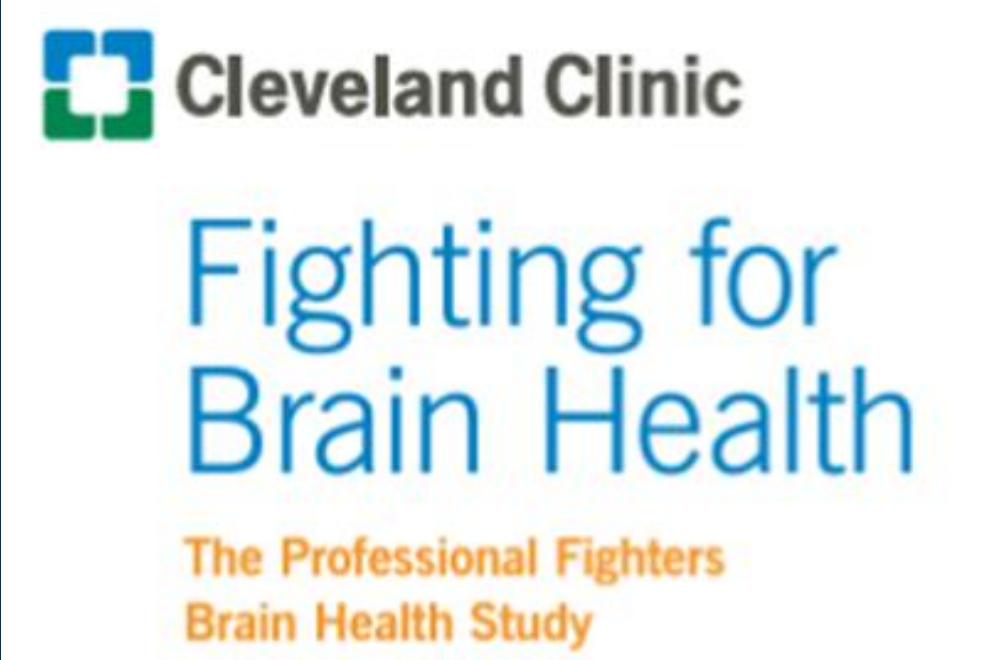




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BACKGROUND

- Professional fighters exposed to repetitive head injury (RHI) experience elevated risk for chronic traumatic encephalopathy (CTE)[1]. Diffusion tensor imaging (DTI) provides sensitive markers of microstructural changes in brain injury.
- Conventional DTI measures are confounded by extracellular free water, particularly in gray matter regions vulnerable to RHI. *Apolipoprotein* E4 carrier status, may further modify brain responses to RHI [2,3]
- This study explores the effect of RHI-exposure and *APOE4* carrier status on free water-corrected (fwc) DTI measures of microstructure.

METHODS

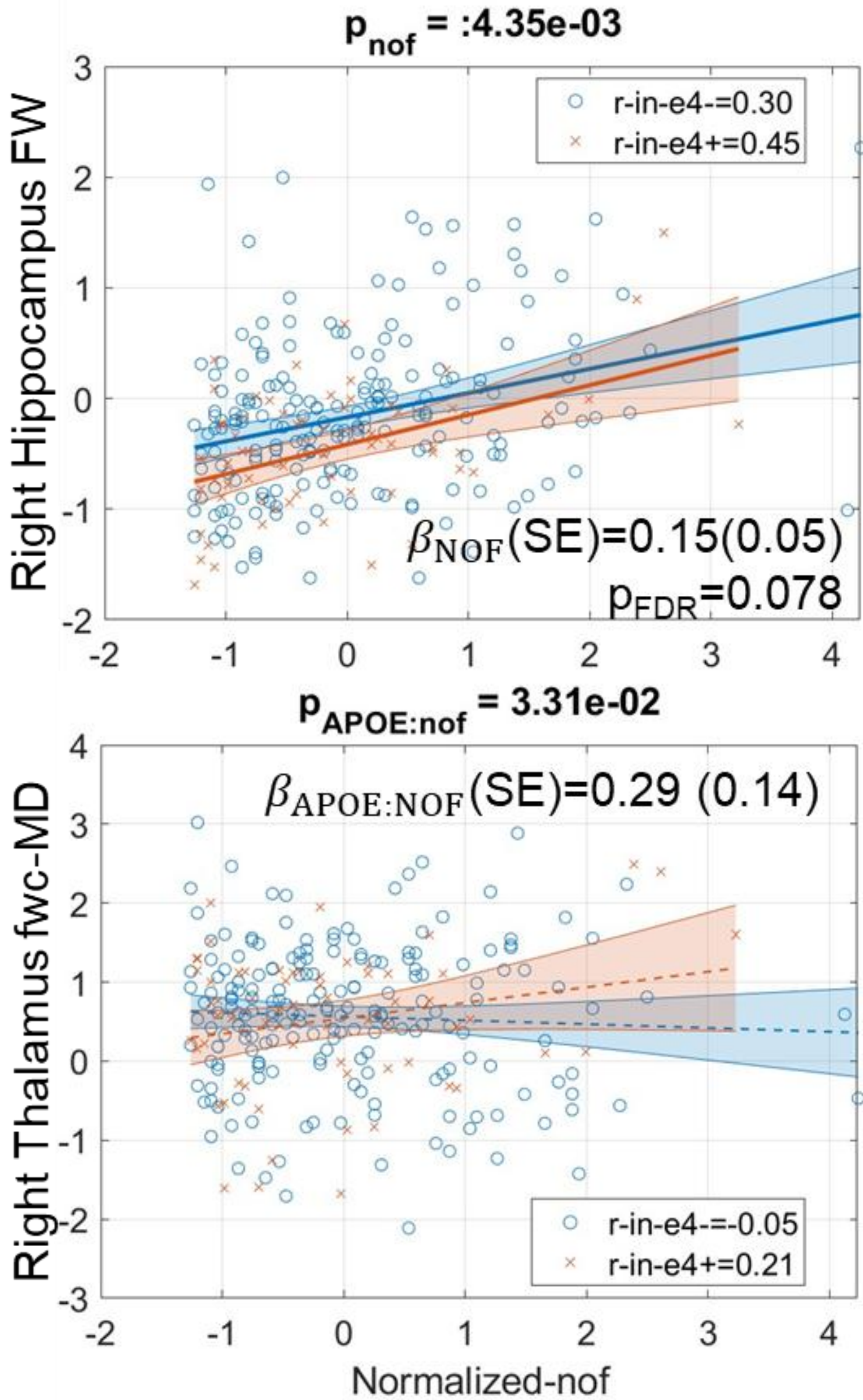
- Participants:** Fighters and mixed martial artists (MMAs) drawn from the **Professional Athletes Brain Health Study (PABHS)**. See Sample Characteristics.
- DTI processing:** b-values=1000s/mm², 71 directions; Corrected for noise, movement, eddy currents[4] and bias; Free-water removed via dual tensor modeling [5].
- DTI measures in subcortical Grey Matter:** Free water fraction (FWF), fwc-Mean Diffusivity (fwc-MD) and Fractional Anisotropy (fwc-FA) in FreeSurfer parcellated, and transformed to DTI space, hippocampus (HC), thalamus (Thal). Regions were preselected based on previous PABHS findings that NOF predicts thalamic/hippocampal volumes.
- Statistical Analyses:** Linear regressions to examine whether *APOE4* carrier status moderates association of DTI measures with NOF.
 - Covariates: age, sex, race, years education, types-of-fighting, recent sparring status, days since last documented fight and regional volumes.
 - Non-significant interaction term was dropped and reduced model was used to evaluate whether DTI measure associated with NOF..
- Models were FDR-corrected for multiple comparisons by number of regions/tracts per effect.

SAMPLE CHARACTERISTICS

Mean(std)	<i>APOE</i> E4 non-carriers	<i>APOE</i> E4 carriers	p-value ¹
N	194	63	
Sex	34 Female 160 Male	5 Female 58 Male	0.07
Age (years)	38.87 (10.28)	37.26 (7.94)	
Race	112 White 37 African American; 45 Others	30 White 23 African American 10 others	0.04
Years of Education	13.50 (2.48)	13.19 (1.97)	
Number of professional fights	23.14 (17.85)	20.33 (17.71)	
Types of fighting	84 Boxing 110 MMA	32 Boxing 31 MMA	
Sparring in the past two weeks	85 yes 88 no 21 Unknown	26 yes 31 no 6 Unknown	
Days since last fight	2051.82 (2835.98)	1463.14 (1997.76)	

¹Chi-square tests for categorical variables and two-sample t-tests for continuous variables

KEY RESULTS SUMMARY



RESULTS

- Greater NOF predicted higher hippocampal FWF, independent of *APOE4* carrier status.
 - APOE4* carrier status moderates association between NOF and fwc-MD of the right thalamus, with positive association seen in E4 carriers only. Both results hold when limit to both Male fighters (Table below) .
- | Effect | Measure | Standardized β (SE) | pValue (p_{FDR}) | Standardized β (SE) in Male |
|----------|---------------|---------------------------|-----------------------------|-----------------------------------|
| NOF:APOE | HC R FWF | - | - | - |
| | Thal R fwc-MD | 0.294 (0.137) | 0.033 (0.312) | 0.323 (0.155) |
| NOF | HC R FWF | 0.146 (0.051) | 0.004 (0.078) | 0.144 (0.055) |
| | Thal R fwc-MD | -0.140 (0.081) | 0.086 | -0.131 (0.092) |
- In this same cohort, NOF further predicts right thalamic volume($\beta_{\text{NOF}}(\text{SE}) = -0.143(0.046)$) and right hippocampal volume ($\beta_{\text{NOF}}(\text{SE}) = -0.145(0.054)$), independent of *APOE4* carrier status.

CONCLUSIONS

- Subcortical-grey matter regions are sensitive to RHI-related tissue changes, as further reflected by significant associations between NOF and DTI measures.
- NOF-DTI measures tend to more sensitive to *APOE4* carrier status.
- Interpretation is limited by the cross-sectional design and inclusion of both active and retired fighters, which may bias associations due to differences in recent exposure and recovery.

ACKNOWLEDGEMENTS

[1] Mckee et al., 2016; [2] Banks et al., 2016' [3] Atherton et al., 2022; [4] Tournier et al., 2019; [5] Pasternak et al., 2009. Research reported in this study was supported by Lincy Foundation, Belator, Ultimate Fighting Championship Company (UFC), the August Rapone Family Foundation, Top Rank, Haymon Boxing, and the National Institutes of Health (NIA-grant 1RF1AG071566, NIGMS-grant P20GM109025 and NIA-grant P20AG068053).