HIV Status and APOE4 Differentially Impact White Matter Integrity in Adults with HIV

586

Peyton Thomas[1], Hannah Walsh[1], R. Craig Gallagher[1], Kyle Shattuck[1,2], Princy Kumar[3], David J. Moore[4], Ronald J. Ellis[4,5], Xiong Jiang[1]
[1]Department of Neuroscience, [2]Department of Rehabilitation Medicine, [3]Department of Medicine, Georgetown University Medical Center, Washington, DC, USA
[4]Department of Psychiatry, [5]Department of Neurosciences, University of California, San Diego, CA, USA

BACKGROUND

- With the current age of people living with HIV (PWH) rapidly increasing, there is a potential overlap and interaction of neurodegenerative and viral processes
- APOE4 genotype is the strongest known genetic risk factor for late onset, sporadic Alzheimer's Disease (AD)
- Aging PWH who also have an APOE4 genotype may be the subpopulation of PWH at highest risk to begin developing signs of AD-like neurodegeneration

Hypotheses:

- HIV status and APOE4 genotype will both negatively impact WM microstructure
- Advanced age and HIV-disease (i.e., log CD4 nadir, disease duration) may additively or even interactively affect WM microstructure

METHODS

- DTI data were collected on a Siemens 3T MRI scanner
- All DTI data was preprocessed in FSL
- Probabilistic tractography on 22 atlas-defined major white matter bundles was run using Automated Fiber Quantification (pyAFQ)
- Fractional anisotropy (FA) and mean diffusivity (MD) were extracted at 100 nodes along each bundle
- Pointwise t-tests with FDR correction were conducted at each node within each bundle for group comparisons
- Post-hoc two-way ANCOVAs were run on significant ROIs to examine the impact of age and disease factors

Participant Demographics:

All Subjects:	HIV+ (n=57)	HIV- (n=18)	Total (n=75)	p-value
Age: M (SD)	56.2 (6.6)	57.7 (5.1)	56.5 (6.3)	0.3
Education: M (SD)	14.6 (2.8)	14.6 (2.6)	14.6 (2.7)	0.93
African-American Race: n (%)	37 (65%)	11 (69%)	48 (64%)	0.77
Sex: Male n (%)	41 (72%)	11 (61%)	52 (61%)	0.38
APOE: *E4+ n (%)	12 (22%)	2 (11%)	14 (19%)	0.73
Disease Duration: M (SD)	26.5 yrs (9.4)	N/A	N/A	N/A
CD4 nadir: M (SD)	224.3 (213.5)	N/A	N/A	N/A

PWH:	E4+ (n=12)	E4- (n=43)	Total (n=57)	p-value
Age: M (SD)	55.3 (6.0)	56.3 (6.9)	56.2 (6.6)	0.64
Education: M (SD)	13.5 (3.3)	14.8 (2.5)	14.6 (2.8)	0.22
African-American Race: n (%)	10 (83%)	25 (58%)	37 (65%)	0.11
Sex: Male n (%)	6 (50%)	34 (79%)	41 (72%)	0.046
Disease Duration: M (SD)	26.2 yrs (10.3)	26.8 yrs (9.5)	26.5 yrs (9.4)	0.86
CD4 nadir: M (SD)	213.7 (192.4)	229.3 (223.6)	224.3 (213.5)	0.81

p-values calculated from chi² or two-sample t-tests; *4 APOE4+ subjects are homozygous carriers

HIV is associated with a widespread increase in mean diffusivity (MD) and a steeper age-related increase in MD

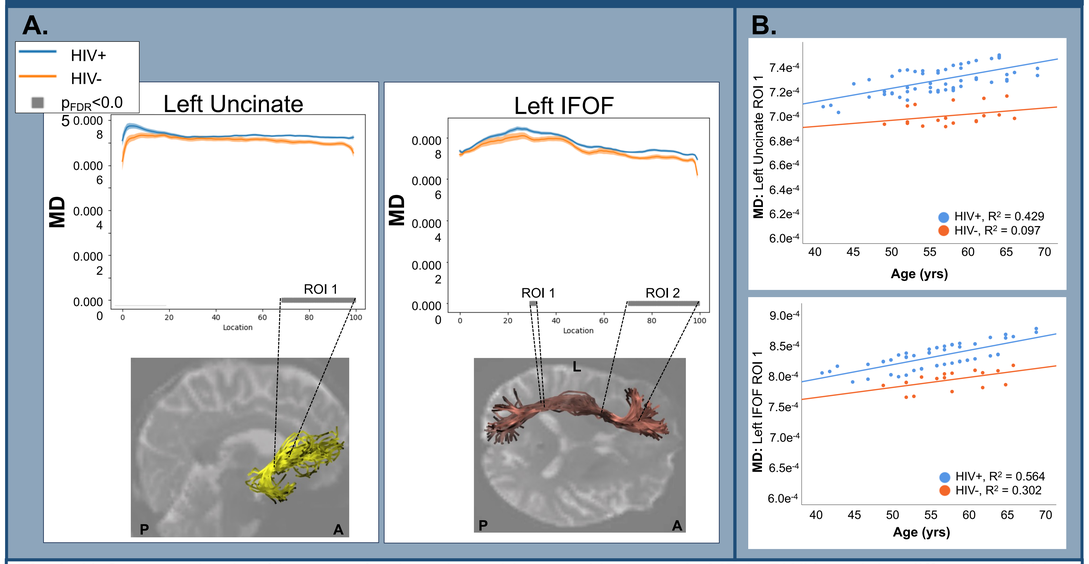


Fig 1. A) Compared to healthy controls, there is a widespread increase in MD in PWH, and the difference within regions of the left inferior frontal orbital fasciculus (IFOF) and left uncinate survives FDR correction. B) Older age is associated with a steeper incline in MD in PHW than controls within these ROIs.

APOE4 is associated with localized reduction in fractional anisotropy (FA), and a steeper FA reduction in PWH with longer disease duration

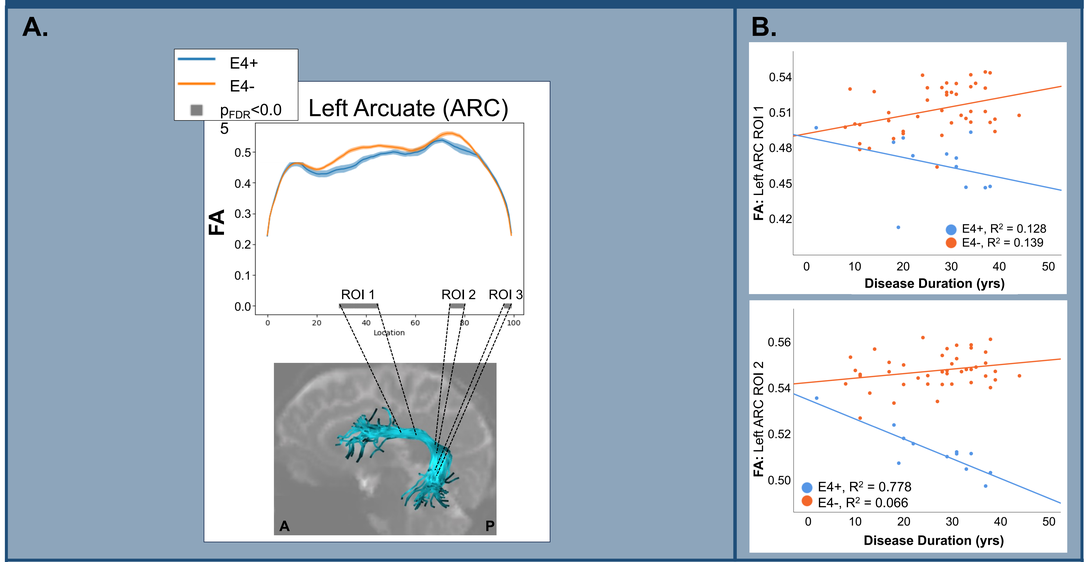


Fig 2. A) Compared to E4-, E4+ subjects had significantly reduced FA within regions of the left arcuate B) Within PWH, there is a significant disease duration x group interaction in 2 regions of the bundle, with longer disease duration linked to smaller FA values in E4 carriers but not in non-carriers.

RESULTS

PWH vs Controls (Fig. 1):

- There is a widespread increase in mean diffusivity (MD) in all bundles in HIV+ compared to HIV- groups, with significant differences in the left uncinate and left IFOF bundles (p_{FDR}<0.05)
- Within regions of the two bundles, age is associated with a steeper increase in MD in PWH than controls:
  - HIV x age interaction in left IFOF ROI 1 ($F(1)$=9.82, p=0.003)
  - HIV x age interaction in left uncinate ROI ($F(1)$=9.67, p=0.003)

E4+ vs E4- (Fig. 2):

- Across PWH and controls, E4+ is associated with lower fractional anisotropy (FA) in the left arcuate, and the E4 effect remains significant with the PWH group
- Within PWH, longer disease duration is associated with lower FA in E4 carriers but not non-carriers:
  - E4 x disease duration interaction in ROIs 1 ($F(1)$=9.93, p=0.003) and 2 ($F(1)$=4.28, p=0.044)

CONCLUSIONS

- Both HIV-disease and age are associated with higher MD, and age-related incline in MD is stronger in PWH than controls
- APOE4 is associated with lower FA, and within PWH longer disease duration is also linked to lower FA, but only in PWH E4 carriers and not in non-carriers

Implications:

- These combined results on WM microstructure indicate a compilation of aging, viral, and genetic processes contributing to decreased WM integrity in populations with HIV
- There is a potential interaction of APOE4 and HIV that could present a heightened risk of Alzheimer's Disease in aging populations with HIV

Future Directions:

- Examine longitudinal changes to better detect temporal trajectory of WM changes
- Apply a more sensitive diffusion analysis to examine both microstructural and macrostructural changes

ADDITIONAL KEY INFORMATION

Contact Information: pt533@georgetown.edu

Acknowledgements:
We would like to thank all the subjects who have dedicated their time to participate in this research project.
Funding:
This work is funded by the National Institutes of Health under grants 1R01MH108466, 1R56NS124422, and 1R01NS124422.