Evaluating White Matter Integrity in Relation to HIV Severity and Cognitive Impairment

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Background

- Though HIV is incurable, **people with HIV (PWH)** who undergo **combination antiretroviral therapy (cART)** are able live with suppressed **viral loads (VL)** undetectable by blood tests.
- cART has prolonged the healthspan of PWH, leading to an older HIV+ population for which age-associated HIV comorbidities such as increased risk of **cognitive impairment (CI)** are of greater concern.
- Though cART has decreased the frequency of HIV-associated dementia in PWH, PWH are still at elevated risk of developing CI compared to **people without HIV (PWoH).**
- The mechanism behind increased CI in PWH remains unknown and has been attributed to a variety of factors, such as chronic inflammation, neuronal loss, and viral protein neurotoxicity.
- HIV has been associated with **white matter (WM)** changes, such as reduced WM integrity and increased WM hyperintensities.
- **Diffusion tensor imaging (DTI)** allows for quantification of white matter structure and integrity through four different metrics: **axial diffusivity (AD), fractional anisotropy (FA), mean diffusivity (MD),** and **radial diffusivity (RD).**
- Prior research studies have found correlations between HIV, CI, and WM using DTI but have presented inconsistent results.

Objectives

This study intends to further investigate the relationship between HIV, CI, and WM by building upon prior research studies with the following adjustments: analyzing all four DTI metrics, separating into three groups (control, undetected VL, and detected VL), studying a larger cohort, and identifying differences between individual WM tracts.

Demographics

Total (N = 304)	Control (N=111)	Undetected (N=139)	Detected (N=54)	Control / Undetected *p*-Value	Control / Detected *p*-Value	Undetected / Detected *p*-Value
Age in Years (SD)	37.9 (16.2)	46.2 (12.9)	44.4 (16.0)	**<0.001****	**0.015***	0.42
Gender (% Male)	55.9%	69.8%	87.0%	0.023*	**<0.001****	**0.013***
Ethnicity				N/A	N/A	N/A
% Caucasian	38.7%	28.1%	33.3%			
% African American	57.7%	71.2%	64.8%			
% Asian	0.9%	0.0%	0.0%			
% American Indian	0.0%	0.0%	1.9%			
% Multiracial	0.9%	0.7%	0.0%			
% Other	1.8%	0.0%	0.0%			
Highest Degree of Education (SD)	13.9 (2.4)	13.0 (2.6)	13.1 (2.3)	0.0042*	0.033*	0.85
Duration of Infection in Months (SD)	N/A	169.8 (106.8)	110.4 (108.8)	N/A	N/A	0.0012*
Recent CD4 Cell Count (SD)	N/A	672.6 (280.5)	467.0 (339.1)	N/A	N/A	<0.001**
Nadir CD4 Cell Count (SD)	N/A	204.8 (166.2)	220.9 (180.6)	N/A	N/A	0.62
Recent Viral Load (SD)	N/A	20.0 (0.0)	21810.1 (55602.0)	N/A	N/A	0.0057*
Recent CD8 Cell Count (SD)	N/A	886.2 (446.8)	847.6 (411.3)	N/A	N/A	0.76
CD4/CD8 Ratio (SD)	N/A	0.9 (0.5)	0.6 (0.4)	N/A	N/A	0.13
Hepatitis C (% Positive)	0.0%	6.5%	3.7%	0.0024*	0.16	0.46

Table 1: Demographics table for research participants, which were recruited through the Washington University School of Medicine's Infectious Disease Clinic, AIDS Clinical Trial Unit, and Supportive Positive Opportunities with Teens Youth Center. Noticeable differences in age and gender were observed, bolded, and treated as covariates in our analysis. Asterisks represent levels of statistical significance. Individuals with a VL of 20 IU/mL or less were considered undetected.

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Methods

CI Data

- Acquired via neuropsychological battery of 15 tests converted to domain-specific *Z*-scores for learning, delayed recall, executive function, psychomotor speed, and language
- Individuals marked as CI with one score less than -2 or two scores less than -1

DTI Data

- Voxelwise analysis performed using tract-based spatial statistics (TBSS) via the Oxford Centre for Functional Magnetic Resonance Imaging of the Brain Software Library (FSL)
    - TBSS aligns all subject data to a standard space, creates a mean WM tract skeleton, and projects DTI data onto the skeleton for cross-subject analysis
    - Performed *F*-contrasts between HIV groups (control, undetected VL, and detected VL) to determine overarching differences followed by *t*-contrasts to identify pairwise relationships
    - Performed *t*-contrasts between CI statuses (impaired and unimpaired) within the undetected group to assess relationship between CI and WM integrity for PWH
    - CI only assessed for HIV+ groups due to large age difference with HIV- group
- DTI values compared between HIV groups across 20 individual WM tracts using R
    - Significance values correct for multiple comparisons

Results

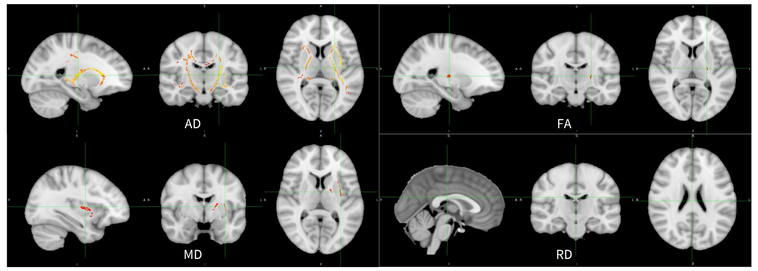


Figure 1 (above): Images of significantly different voxels for *F*-contrasts ran between HIV groups. Correction for multiple comparisons was performed and the *p*-value was set at 0.05 corrected. AD, FA, and MD produced significant results, but RD did not. Significant voxels are colored in a gradient with yellow and red representing smaller and greater *p*-values, respectively.

Contrast Comparison	AD	FA	MD	RD
Control > Undetected	**Significant**	Insignificant	Insignificant	Insignificant
Undetected > Control	Insignificant	Insignificant	Insignificant	Insignificant
Control > Detected	Insignificant	Insignificant	Insignificant	Insignificant
Detected > Control	Insignificant	**Significant**	Insignificant	Insignificant
Undetected > Detected	Insignificant	Insignificant	Insignificant	Insignificant
Detected > Undetected	**Significant**	Insignificant	**Significant**	Insignificant

Table 2 (above): Table of results for *t*-contrasts ran between HIV groups with the *p*-value set at 0.05. The four significant results are bolded in the table for visual clarity

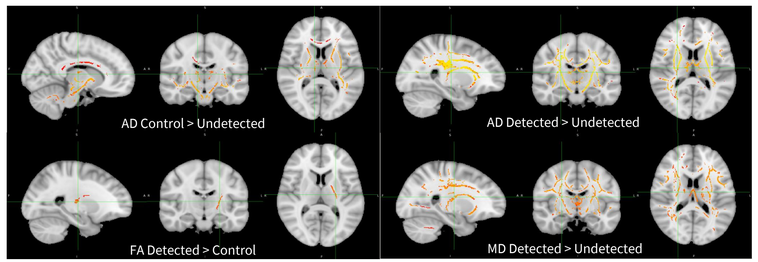


Figure 2: Images for *t*-contrasts that produced significant results.

Results

Contrast Comparison	AD	FA	MD	RD
Undetected Unimpaired > Undetected Impaired	Insignificant	Insignificant	Insignificant	Insignificant
Undetected Impaired > Undetected Unimpaired	Insignificant	Insignificant	Insignificant	Insignificant

Table 3 (above): Table of results for *t*-contrasts ran between CI statuses for the undetected group with the *p*-value set at 0.05. No significant results were produced.

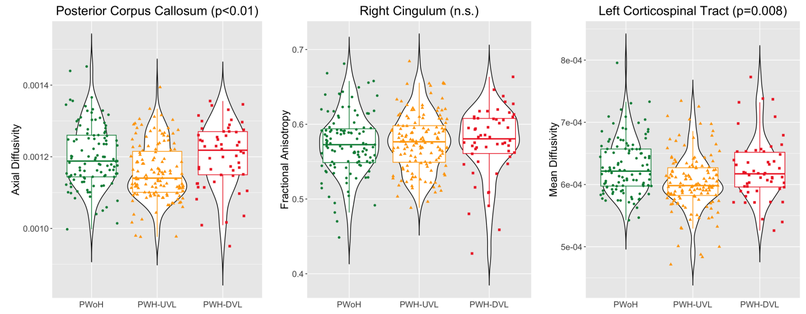


Figure 3 (above): Plots of different DTI metric values across HIV groups for individual white matter tracts. One representative plot corresponding to a single white matter tract was created for each DTI metric that produced at least one significant results from Table 2.

Region of Interest	AD	FA	MD	RD
Posterior Corpus Callosum	**0.009***	0.919	**0.034***	0.446
Corticospinal Tract Left	**<0.001****	0.919	**0.008***	0.446
Left Cingulum	**0.035***	0.380	0.178	0.450
Perforant Pathway Left	**0.035***	0.369	0.430	0.781

Table 4 (above): Table of *p*-values for different DTI metrics compared between HIV groups across individual WM tracts. Only regions of interest with at least one significant result are included. Regions of interest that are not included are the anterior corpus callosum, corticospinal tract right, forceps major, forceps minor, frontal aslant tract left, front aslant tract right, frontal occipital fasciculus left, front occipital fasciculus right, inferior longitudinal fasciculus left, inferior longitudinal fasciculus right, perforant pathway right, right cingulum, superior longitudinal fasciculus left, superior longitudinal fasciculus right, uncinate fasciculus left, and uncinate fasciculus right. Significant values are bolded for visual clarity. Asterisks represent levels of statistical significance. Of note is that no individual WM tracts produced significant results for FA unlike in Figure 1.

Conclusions

- No differences in DTI metrics found between CI statuses in undetected PWH
    - Unable to conclude that WM integrity is the mechanism by which CI in PWH is derived
- Differences in AD and MD between detected and undetected groups
    - Increased diffusion in detected group
    - Detected PWH appear to have worse WM integrity than undetected PWH as is expected given that HIV has been found to associate with WM deterioration
    - Resembles trends associated with inflammation from previous research study
    - Unable to confirm due to lack of inflammation data
- Differences in FA between control and detected groups
    - Only appears in internal capsule region
    - Unvalidated by tractwise plots possibly due to small region of significant voxels being split between multiple WM tracts
- Differences in AD between control and undetected groups
    - Unexpected finding
    - Could possibly be attributed to large age difference between the two groups

Future Directions

- Obtain diffusion basis spectrum imaging or biomarker data to address inflammation hypothesis
- Incorporate additional control subjects to address the larger age difference between HIV+ and HIV- groups and allow for more fair comparisons

For further questions Email: **strainj@wustl.edu**