Synaptic Density Loss by Brain Regions in People with Chronic HIV

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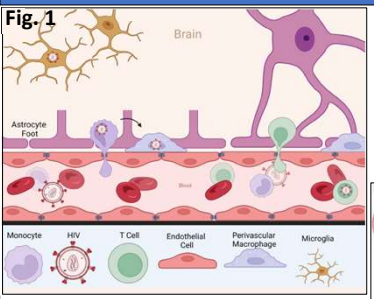
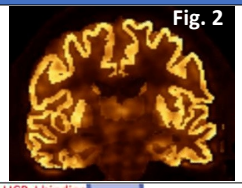
Abstract

HIV crosses the blood-brain barrier through infected CD4+ T-cells early in acute infection and creates reservoirs of virus in the brain. These reservoirs are untreatable by antiretroviral therapy (ART). ART has improved health outcomes and life expectancy for people living with HIV (PLWH), but cognitive decline and loss of synaptic density still present earlier in PLWH than in HIV-uninfected individuals due to neurological injury caused by infection. We used novel PET imaging of synaptic vesicle protein 2A (SV2A) to investigate regional synaptic density across brain lobes in PLWH and HIV-uninfected participants to identify patterns in proliferation of neurological injury and potential comorbidities. PET measurements of binding potential (BPND) indicated similar loss of synaptic density across all brain regions in PLWH.





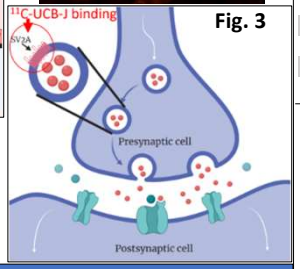


Fig. 1: HIV crosses the blood-brain barrier using immune cells. **Fig. 2:** PET image reflecting synapse concentrations. **Fig. 3:** 11C-UCB-J binding site on synaptic vesicle.

Methods

Positron Emission Tomography (PET)

Radiolabeled ligand ("tracer") is infused into blood, binds its receptor. PET imaging detects radioactive decay and constructs an image showing the radioligand distribution.

C-UCB-J PET tracer to measure SV2A as a marker of synaptic density

SV2A (synaptic vesicle glycoprotein 2) is ubiquitously present in presynaptic nerve terminals throughout the brain. SV2A concentration reflects synaptic density. 11C-UCB-J is a PET tracer that binds to SV2A and has been validated as the first measure of synaptic density in living humans. (Fig. 2.)

Data Analysis

IBM SPSS Statistics software was used in data analysis to perform Mann Whitney-U tests comparing BPND between PLWH and Healthy controls. Correlation heatmaps were used to identify comorbidities associated with changes in synaptic density.

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References

[1] J. J. Weiss et al., "Preliminary In Vivo Evidence of Reduced Synaptic Density in Human Immunodeficiency Virus (HIV) Despite Antiretroviral Therapy"
[2] Z. Cai, S. Li, D. Matuskey, N. Nabulsi, and Y. Huang, "PET Imaging of Synaptic Density: A New Tool for Investigation of Neuropsychiatric Diseases"

Table 1. Demographics and Clinical Characteristics of Participants

Demographic characteristic	HIV (*n* = 15)	HIV-uninfected Participants (*n* = 13)
Male sex, no. (%)	14 (93)	13 (100)
Age, mean (SD), y	58.5 (5.9)	57.3 (6.8)
Non-White race, no. (%)	11 (73)	4 (31)
Hispanic, no. (%)	1 (7)	0 (0)
BMI, mean (SD), kg/m²	30.3 (6.3)	29.2 (3.1)
Education, mean (SD), y[b]	13.8 (2.9)	15.1 (1.7)
History of SUD, no. (%)	8 (53)	N/A
History of AUD, no. (%)	5 (33)	N/A
Smoking		
Current, no. (%)	5 (33)	N/A
Former, no. (%)	9 (60)	N/A
HIV-specific characteristic		
CD4⁺ T cells, median (IQR), cells/μL	697 (555, 875)	
CD4⁺/CD8⁺ ratio, mean (SD)	1.12 (0.50)	
CD4⁺ nadir, median (IQR), cells/μL	209 (83, 375)	
Plasma HIV RNA < 20 copies/mL, no. (%)	13 (87)	
Duration of HIV infection, mean (SD), y	21 (7.6)	
Duration of ART, median (IQR), y	21 (13, 24)	
EPIC Comorbidities		
None, no. (%)	3 (20)	N/A
Type 1 Diabetes, no. (%)	1 (7)	N/A
Type 2 Diabetes, no. (%)	1 (7)	N/A
Mental Health, no. (%)	8 (53)	N/A
Hypertension, no. (%)	4 (27)	N/A
Hyperlipidemia, no. (%)	3 (20)	N/A
Thyroid Disease, no. (%)	2 (13)	N/A
Obesity, no. (%)	1 (7)	N/A

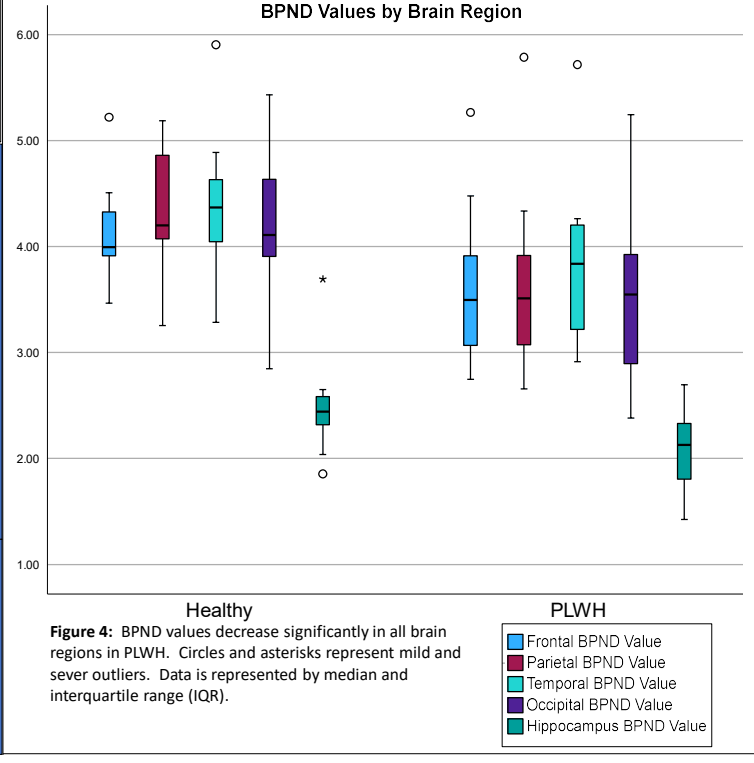

Figure 4: BPND values decrease significantly in all brain regions in PLWH. Circles and asterisks represent mild and sever outliers. Data is represented by median and interquartile range (IQR).

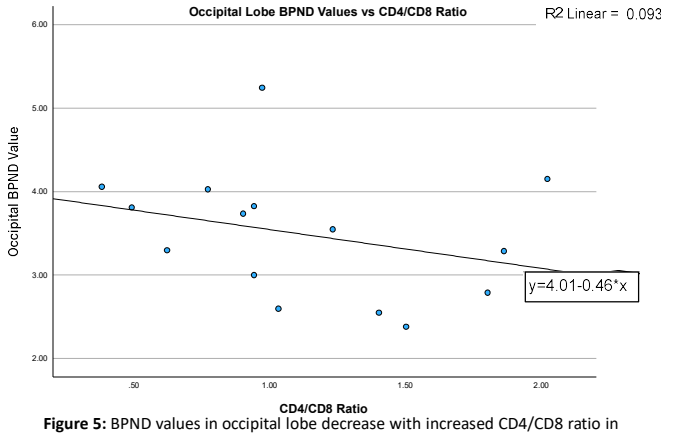

Figure 5: BPND values in occipital lobe decrease with increased CD4/CD8 ratio in PLWH.

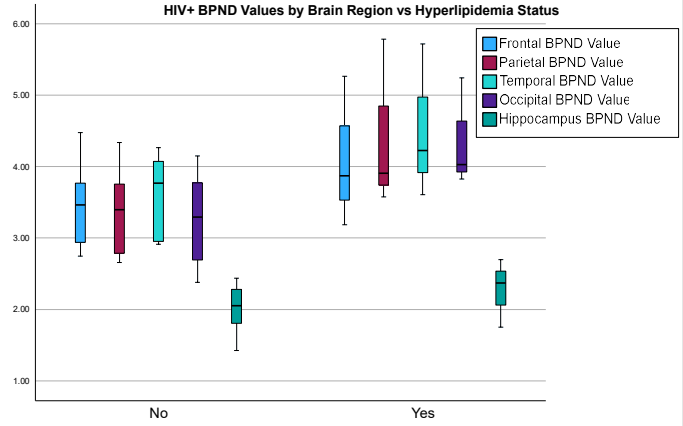

Figure 6: Hyperlipidemia correlates with higher BPND scores across all regions in PLWH.

Results and Conclusions

- Synaptic density loss is consistent across brain regions. No single region exhibits significantly greater loss relative to others. (Fig. 4)
- Increase in CD4/CD8 ratio is correlated with decrease in BPND with a weak R^2 value. (Fig. 5.)
- Hyperlipidemia is strongly correlated with increase of BPND in Occipital and Parietal in PLWH. (Fig. 6)
- The lack of clinical histories for control group participants is a limitation on this study that makes it difficult to separate out the relative influence of comorbidities.

Future directions

- Collect clinical histories for control group participants.
- Investigate the relationship between CD4/CD8 ratio and synaptic density in a longitudinal study.
- Investigate the influence of hyperlipidemia and HIV on synaptic density in a longitudinal study.