LOW CD4 NADIR EXACERBATES THE IMPACTS OF APOE ε4 ON MEMORY CIRCUITRY IN ADULTS WITH HIV

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BACKGROUND

- Nearly 50% of people with HIV (PWH) in the US are 50 or older
- Aging is recognized as a major risk factor for HIV-associated neurocognitive disorders (HAND) as well as other types of dementias, particularly Alzheimer's disease (AD)
- However, the potential interaction between HIV-disease and Alzheimer's disease on brain function remains an open, but increasingly pressing question with a rapidly aging HIV+ populace
- APOE ε4 is the strongest genetic risk factor for late-onset AD
- In HIV-negative cognitively normal adults, ε4 is associated with reduced memory and decreased functional connectivity (FC) between caudate, hippocampus, and other regions in the Papez circuit[1]
- The present study was conducted to understand how HAND and AD may concomitantly affect brain function by studying the impact of APOE ε4 on brain function and the putative interaction between ε4 and HIV disease severity, with a focus on the FCs between caudate, hippocampus, and other regions in the Papez circuit

Predictions: **In PWH, APOE ε4 is associated with reduced memory performance and memory network disruptions, and HIV disease severity may exacerbate the impacts of ε4.**

METHODS

- 99 PWH (56.2±6.5yrs, 41-70yrs, 27 females)
- A comprehensive neuropsychological test battery to assess neurocognitive function and HAND status
- Structural MRI and resting-state functional MRI were collected to assess brain structure and functional connectivity (FC), respectively
- Data analysis: MATLAB, SPM12, CONN, CAT12, ASHS[3], SPSS, and PROCESS

RESULTS

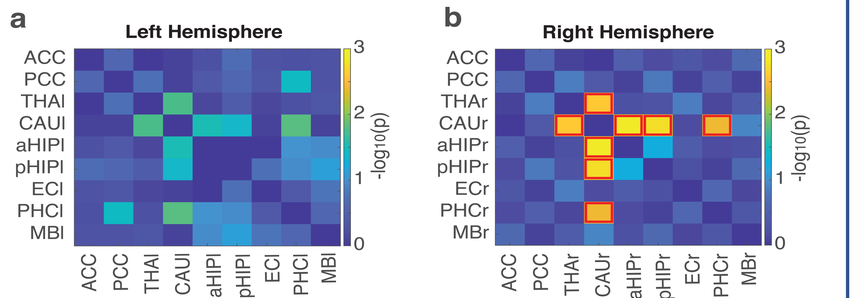
	Carriers (n=26)	Noncarriers (n=66)	p-value
Age (yrs)	55.1 (5.9)	56.6 (6.7)	n.s.
Education (yrs)	13.7 (3.1)	14.5 (2.9)	n.s.
Sex (Female%)	26.9%	21.9%	n.s.
Race (AA%)	76.9%	56.2%	n.s.
CD4 nadir (cells/μl)	152 (330)	200 (285)	n.s.
GDS	0.34 (0.30)	0.36 (0.45)	n.s.
HAND diagnosis	30.8%	28.8%	n.s.
HVLT-R: Delayed Recall	6.96 (2.6)	8.63 (2.5)	0.035
HVLT-R: Retention	74.3 (18.6)	85.8 (15.3)	0.003#
Undetectable Viral Load	84.6%	82.2%	n.s.

HIV+ APOE ε4 carriers with *a history of severe immunosuppression* may be at a **higher risk of Alzheimer's disease** or **other types of dementias** in late life:

- *APOE ε4* may be a **genetic risk factor** for memory impairment in people with HIV

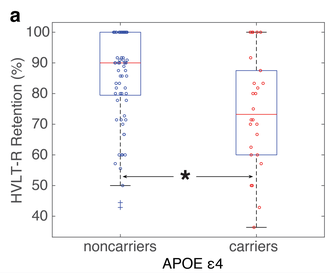
- *History of HIV disease* severity may **exacerbate** the effects of ε4 on brain function and network

Reduced FCs between the right caudate and several regions in the Papez circuitry in ε4 carriers compared to noncarriers (■ indicate p<0.05 after corrected for multiple comparison)

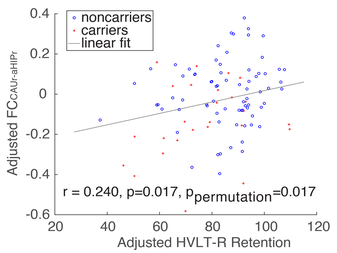


Abbreviations: ACC/PCC, anterior/posterior cingulate cortex; aHIP/pHIP, anterior/posterior hippocampus; CAU, caudate; FC, functional connectivity; FDR, false discovery rate; MB, mammillary body; OC, occipital cortex; ROI, region-of-interest; PUT, putamen. THA, thalamus; -l/-r: left/right (e.g., CAUl/CAUr, left and right caudate, respectively).

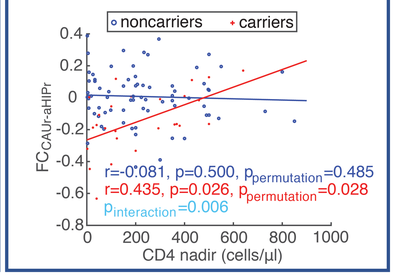
ε4 carriers had lower HVLT-R delayed recall and retention rate scores than noncarriers



FC between CAUr and aHIPr ($FC_{CAUr\text{-}aHIPr}$) correlated HVLT-R retention rate



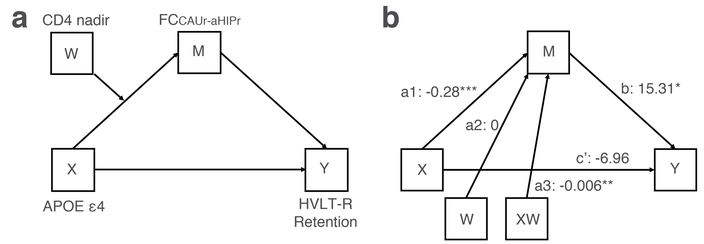
A strong interaction between APOE ε4 status and CD4 nadir counts on $FC_{CAUr\text{-}aHIPr}$



Note: demographics (age, edu, sex, and race) were controlled in all analyses.

The moderated mediation analysis: (a) the concept model; (b) the statistical diagram model of significance. Two key findings:

- ε4 was associated with reduced caudate-hippocampus FC ($FC_{CAUr\text{-}aHIPr}$), but the association was moderated by nadir CD4, i.e., the $FC_{CAUr\text{-}aHIPr}$ was lower in ε4 carriers than noncarriers, but only when CD4 nadir was low
- ε4 had an indirect detrimental effect on memory performance through $FC_{CAUr\text{-}aHIPr}$, but the indirect effect was conditional on CD4 nadir, i.e., the indirect effect of ε4 was significant when CD4 nadir was low (<=199 cells/μl), but not when CD4 nadir was high (>=463 cells/μl).



CONCLUSIONS

- ε4 is associated with worse memory performance and disruptions to the memory network
- The network disruption correlates with memory performance
- Caudate (but not hippocampus) may play a predominant role in this functional disruption, in line with the critical role of caudate in HAND[2]
- The severity of HIV disease (i.e., low CD4 nadir) may exacerbate the effects of ε4 on the brain in PWH

REFRERENCE

1. Li W, et al. (2014). Aberrant functional connectivity in Papez circuit correlates with memory performance in cognitively intact middle-aged APOE4 carriers. Cortex.

2. Israel, S. M., et al. (2019). Different roles of frontal versus striatal atrophy in HIV-associated neurocognitive disorders. Human brain mapping.

3. Xie, L., et al. (2019). Automated segmentation of medial temporal lobe subregions on in vivo T1-weighted MRI in early stages of Alzheimer's disease. Human brain mapping.

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