UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Assessing brain morphology and inflammation in relation to episodic memory profiles among aging adults with HIV

A dissertation submitted in partial satisfaction
of the requirements for the degree of Doctor of Philosophy

in

Clinical Psychology

by

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LIST OF ABBREVIATIONS

AD = Alzheimer's disease
AIDS = acquired immunodeficiency syndrome
aMCI = amnestic mild cognitive impairment
ART = antiretroviral therapy
Aβ = amyloid beta
BVMT-R = Brief Visuospatial Memory Test-Revised
CCL2 = chemokine (C-C motif) ligand 2/monocyte chemoattractant protein-1
CHARTER = CNS HIV Anti-Retroviral Therapy Effects Research
CNS = central nervous system
CRP = C-reactive protein
CSF = cerebrospinal fluid
CXCL10 = C-X-C motif chemokine 10/interferon-gamma-inducible protein-10
HAND = HIV-associated neurocognitive impairment
HCV = Hepatitis C
HIV = human immunodeficiency virus
HNRP = HIV Neurobehavioral Research Program at UC San Diego
HVLT-R = Hopkins Verbal Learning Test-Revised
ICV = intracranial volume
IL-6 = interleukin-6
MCI = mild cognitive impairment
MRS = magnetic resonance spectroscopy
MRI = magnetic resonance imaging
MTL = medial temporal lobe
PWH = people with HIV
ROI = regions of interest
TNF-α = tumor necrosis factor-alpha

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ACKNOWLEDGMENTS

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VITA

EDUCATION

2017 – 2023 **Doctor of Philosophy (Ph.D.) in Clinical Psychology**
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2017 – 2019 **Master of Science (M.S.) in Clinical Psychology**
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2010 – 2014 **Bachelor of Science (B.S.)**
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GRANTS AND FELLOWSHIPS

2021 – 2022 **Diana Jacobs Kalman/American Federation for Aging Research (AFAR) Scholarship for Research in the Biology of Aging**
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HONORS AND AWARDS

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2017 Honorable Mention - National Sciences Foundation (NSF) Graduate Research Fellowship Program

RESEARCH PUBLICATIONS

Peer Reviewed Papers

1. Delgadillo, J., **Campbell, L. M.,** Marquine, M., Heaton, A., Rooney, A., Umlauf, A., Jeste, D., Moore, D. J., & Moore R. C. (*in press*). Higher religiosity and spirituality are associated with ethnic group membership among middle-aged and older adults living with HIV. *HIV Research & Clinical Practice.* Epub ahead of print. doi: 10.1080/25787489.2022.2113962

2. Moore, R. C., Ackerman, R. A., Russell, M. T., **Campbell, L. M.,** Depp, C. A., Harvey, P. D., & Pinkham, A. E. (2022). Feasibility and validity of ecological momentary cognitive testing among older adults with mild cognitive impairment. *Frontiers in Digital Health.* Epub ahead of print. doi: 10.3389/fdgth.2022.946685

3. **Campbell, L. M.,** Montoya, J. L., Fazeli, P. L., Marquine, M. J., Ellis, R. J., Jeste, D. V., Moore, D. J., & Moore, R. C. (2022). Association between VACS Index and health related quality of life in persons with HIV: Moderating role of fruit and vegetable consumption. *International Journal of Behavioral Medicine.* Epub ahead of print. doi: /10.1007/s12529-022-10096-4

4. Saloner, R., Lobo, J. D., Paolillo, E. W., **Campbell, L. M.,** Letendre, S. L., Cherner, M., Grant, I., Heaton, R. K., Ellis, R. J., & Moore, D. J. (2022). Cognitive and physiologic reserve uniquely relate to superior neurocognitive abilities in adults aging with HIV. *Journal of Acquired Immune Deficiency Syndromes*. *90*(4), 440-448. doi: 10.1097/QAI.0000000000002988

5. **Campbell, L. M.,** Sun-Suslow, N., Heaton, A., Heaton, R. K., Ellis, R. J., Moore, D. J., & Moore, R. C. (2022). Fatigue is associated with worse cognitive and everyday functioning in older persons with HIV. *AIDS. 36*(6), 763-772. doi: 10.1097/qad.0000000000003162

6. Zlatar, Z. Z., **Campbell, L. M.,** Tang, B., Gabin, S., Heaton, A., Higgins, M., Swendsen, J., Moore, D. J., & Moore, R. C. (2022). Daily level association of physical activity and performance on ecological momentary cognitive tests in free-living environments: A mobile health observational study. *JMIR mHealth and uHealth, 10*(1), e33747. doi: 10.2196/33747

7. **Campbell, L. M.,** Kohli, M., Lee, E. E., Kaufmann, C. N., Higgins, M., Delgadillo, J. D., Heaton, R. K., Cherner, M., Ellis, R. J., Moore, D. J., & Moore, R. C. (2022). Objective and subjective sleep measures are associated with neurocognition in aging adults with and without HIV. *The Clinical Neuropsychologist. 36*(6), 1352-371. doi: 10.1080/13854046.2020.1824280

8. Sun-Suslow, N., Balon, E., Montoya, J., Saloner, R., **Campbell, L. M.,** Serrano, V., Ellis, R. J., & Moore, D. J. (2021). Frailty syndrome is associated with poorer self-reported sleep

quality among older persons with Human Immunodeficiency Virus. *AIDS Research and Human Retroviruses*. *32*(2), 87-96. doi: 10.1089/AID.2020.0158

9. Saloner, R., Lobo, J. D., Paolillo, E. W., **Campbell, L. M.,** Letendre, S. L., Cherner, M., Grant, I., Heaton, R. K., Ellis, R. J., Roesch, S. C., & Moore, D. J. (2021). Identification of youthful neurocognitive trajectories in adults aging with HIV: A latent growth mixture model. *AIDS and Behavior*. *26*(6), 1966-1979. doi: 0.1007/s10461-021-03546-9

10. Serrano, V., Montoya, J. L., **Campbell, L. M.,** Sundermann, E., Iudicello, J., Letendre, S., Heaton, R. K., & Moore, D. J. (2021). The relationship between vascular endothelial growth factor (VEGF) and amnestic mild cognitive impairment among older adults living with HIV. *Journal of NeuroVirology. 27*(6), 885-894. doi: 10.1007/s13365-021-01001-7

11. Sun-Suslow, N., **Campbell, L. M.,** Tang, B., Fisher, A. C., Lee, E., Paolillo, E., Heaton, A., & Moore, R. C. (2021). Use of digital health technologies to examine subjective and objective sleep with next-day cognition and daily indicators of health in person with and without HIV. *Journal of Behavioral Medicine. 45*(1), 62-75. doi: 10.1007/s10865-021-00233-x

12. Watson, C. W-M., **Campbell, L. M.,** Sun-Suslow, N., Hong, S., Umlauf, A., Ellis, R. J., Iudicello, J. E., Letendre, S., Marcotte, T. D., Heaton, R. K., Morgan, E. E., & Grant, I. (2021). Daily cannabis use is associated with lower CNS inflammation in people with HIV. *Journal of the International Neuropsychological Society, 27*(6), 661-672. doi: 10.1017/S1355617720001447

13. Pasipanodya, E., Montoya, J. L., **Campbell, L. M.,** Hussain, M. A., Saloner, R., Paolillo, E. W., Jeste, D. V., Letendre, S. L., McCutchan, J. A., Heaton, R. K., & Moore, D. J. (2021). Metabolic risk factors as differential predictors of profiles of neurocognitive impairment among older HIV+ and HIV- adults. *Archives of Clinical Neuropsychology, 36*(2)*,* 151-164. doi: 10.1093/arclin/acz040

14. Kamalyan, L., Yang, J., Pope, C. N., Paolillo, E. W., **Campbell, L. M.,** Tang, B., Marquine, M.J., Depp, C. A., & Moore, R. C. (2021). Increased social interactions reduce the association between constricted life-space and lower daily happiness in older adults with and without HIV: A GPS and ecological momentary assessment study. *The American Journal of Geriatric Psychiatry, 29*(8), 867-879. doi: 10.1016/j.jagp.2020.11.005

15. Sundermann, E. E., Bondi, M. W., **Campbell, L. M.,** Gouaux, B., Moore, R. C., Soontornniyomkij, V., Moore, D. J., and the HNRP Group. (2021). Distinguishing amnestic mild cognitive impairment from HIV-associated neurocognitive disorders. *Journal of Infectious Diseases, 224*(3)*,* 435-442. doi: 10.1093/infdis/jiaa760

16. Moore, R. C., Paolillo, E. W., Sundermann, E. E., **Campbell, L. M.,** Delgadillo, J., Heaton, A., Swendsen, J., & Depp, C. A. (2021). Validation of the Mobile Verbal Learning Test: Illustration of its use for age and disease-related cognitive deficits. *International Journal of Methods in Psychiatric Research, 30*(1), e1859. doi: 10.1002/mpr.1859

17. **Campbell, L. M.,** Paolillo, E. W., Bryan, R., Marquie-Beck, J., Moore, D. J., Nebeker, C., & Moore, R. C. (2020). Informing informed consent for HIV research. *Journal of Empirical Research on Human Research Ethics, 15*(4)*,* 235-243. doi: 10.1177/1556264620933766

18. **Campbell, L. M.,** Paolillo, E. W., Heaton, A., Tang, B., Depp, C. A., Granholm, E., Heaton, R. K., Swendsen, J., Moore, D. J., & Moore, R. C. (2020). Daily activities related to mobile cognitive performance in middle-aged and older adults: An ecological momentary cognitive assessment study. *JMIR mHealth and uHealth, 8*(9), e29589. doi: 10.2196/19579

19. Moore, R. C., **Campbell, L. M.,** Delgadillo, J. D., Paolillo, E. W., Sundermann, E. E., Holden, J., Swartz, P., Heaton, R. K., & Swendsen, J., (2020). Smartphone-based measurement of executive function in older adults with and without HIV. *Archives of Clinical Neuropsychology, 35*(4)*,* 347-357. doi: 10.1093/arclin/acz084

20. **Campbell**, **L. M.,** Tang, B., Watson, C. W.-M., Higgins, M., Cherner, M., Henry, B. L., & Moore, R. C. (2020). Cannabis use is associated with greater total sleep time in middle-aged and older adults with and without HIV: A preliminary report utilizing digital health technologies. *Cannabis, 3*(2)*,* 180-189. doi: 10.26828/cannabis.2020.02.005

21. Saloner R., **Campbell L. M.,** Serrano, V., Montoya, J. L., Pasipanodya E., Paolillo E. W., Franklin, D., Ellis, R. J., Letendre, S., Collier, C. C., Clifford, D. B., Gelman, B. B., Marra, C. M., McCutchan, A., Morgello, S., Sacktor, N., Jeste, D. V., Grant, I., Heaton, R. K., Moore, D. J., & the CHARTER and HNRP Groups (2019). Neurocognitive SuperAging in older adults living with HIV: Demographic, neuromedical and everyday functioning correlates. *Journal of the International Neuropsychological Society, 25*(5)*,* 507-519. doi: 10.1017/S1355617719000018

22. Montoya, J. L., **Campbell, L. M.,** Paolillo, E. W., Ellis, R. J., Letendre, S. L., Jeste, D. V., & Moore, D. J. (2019). Inflammation relates to poorer complex motor performance among adults living with HIV on suppressive antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes, 80*(1), 15-23. doi: 10.1097/QAI.00000000001881

23. Paolillo, E. W., Saloner, R., Montoya, J. L., **Campbell, L. M.,** Pasipanodya, E., Iudicello, J. E., Moore, R. C., Letendre, S. L., Jeste, D. V., & Moore, D. J. (2019). Additive effects of HIV and lifetime methamphetamine use disorder on frailty: Associations with neurocognitive and everyday functioning. *AIDS Research and Human Retroviruses*, *35*(11), 1044–1053. doi: 10.1089/AID.2019.0062.

24. **Campbell, L. M.,** Fennema-Notestine, C., Saloner, R., Hussain, M., Chen, A., Franklin, D., Umlauf, A., Ellis, R. J., Collier, A. C., Marra, C. M., Clifford, D. B., Gelman, B. B., Sacktor, N., Morgello, S., McCutchan, J. A., Letendre, S., Grant, I., Heaton, R. K. & the CHARTER Group. (2019). Use of neuroimaging to inform optimal neurocognitive criteria for detecting HIV-associated brain abnormalities. *Journal of the International Neuropsychological Society, 26*(2)*,* 147-162. doi: 10.1017/S1355617719000985

25. Saloner, R., Heaton, R. K., **Campbell**, **L. M.,** Chen, A., Franklin, D., Ellis, R. J., Collier, A., Marra, C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., McCutchan, J. A., Letendre, S., Grant, I., Fennema-Notestine, C., & The CHARTER Group (2019). Effects of comorbidity burden and age on brain integrity in HIV. *AIDS, 33*(7), 1175-1185. doi: 10.1097/QAD.0000000000002192

26. Zlatar, Z. Z., Hays, C., Mestre, Z., **Campbell, L. M.,** Meloy, M. J., Bangen, K. J., Liu, T. T., Kerr, J., & Wierenga, C. E. (2019). Dose-response of accelerometer-measured physical activity and sedentary time on cerebral blood flow in aging. *Experimental Gerontology, 125*(10), 110679. doi: 10.1016/j.exger.2019.110679

27. Hays, C. C., Zlatar, Z. Z., **Campbell, L. M.,** Meloy, M. J., & Wierenga, C. E. (2018). Subjective cognitive decline modifies the relationship between cerebral blood flow and memory function in cognitively normal older adults. *Journal of the International Neuropsychological Society, 24*(3)*,* 213-223. doi: 10.1017/S135561771700087X

28. Eppig, J., Edmonds, E., **Campbell, L. M.,** Sanderson-Cimino, M., Delano-Wood, L., & Bondi, M. (2017). Statistically derived subtypes and associations with cerebrospinal fluid and genetic biomarkers in mild cognitive impairment: A latent profile analysis. *Journal of the International Neuropsychological Society*, *23*(7)*,* 564-576. doi: 10.1017/S135561771700039X

29. Hays, C. C., Zlatar, Z. Z., **Campbell, L. M.**, Meloy, M. J., Wierenga, C. E. (2017). Temporal gradient during famous face naming is associated with lower cerebral blood flow in cognitively normal older adults. *Neuropsychologia, 107*(1)*,* 76-83. doi: 10.1016/j.neuropsychologia.2017.11.011

Commentaries

30. Song, Y., **Campbell, L. M.,** & Moore, R. C. (2021). Future directions for sleep and cognition research in at-risk older adults. *International Psychogeriatrics, 33*(7)*,* 655-658. doi: 10.1017/S1041610220003828

Invited Book Chapters

1. **Campbell, L. M.,** Moore, R. C., & Marquine, M. (*in press*). HIV and aging. In B. J. Sadock, V. A. Sadock, & P. Ruiz (Eds.), *Kaplan and Sadock's comprehensive textbook of psychiatry (11th ed.).* Wolters Kluwer Health.

2. Moore, D. J., Moore, R. C., **Campbell, L. M.,** & Atkinson, J. H. (2022). The influence of depression on cognition and daily functioning. In T. Marcotte, M. Schmitter-Edgecombe & I. Grant (Eds.), *Neuropsychology of everyday functioning (2nd ed.).* Guilford Press.

3. Moore, R. C., Straus, E. S., & **Campbell, L. M.** (2020). Stress, mental health, and aging. In N. Hantke, A. Etkin, & R. O'Hara (Eds.), *Handbook of mental health and aging (3rd ed.,* pp. 37-58). Academic Press.

CONFERENCE ORAL PRESENTATIONS

1. **Campbell, L. M.,** Kohli, M., Sundermann, E. E., Fennema-Notestine, C., Barrett, A., Bloss, C., Bondi, M. W., Clifford, D., Ellis, R. J., Franklin, D., Gelman, B., Grant, I., Heaton, R. K., Letendre, S., Patel, P. B., Moore, D. J., Morgello, S. & Moore, R. C. (2023, February). The relationship between apolipoprotein-E4 genotype, memory, and the medial temporal lobe. Accepted for oral presentation at the 51st meeting of the International Neuropsychological Society in San Diego, CA.

2. Henry, B. L., **Campbell, L. M.,** Montoya, J. L., Paolillo, E. W., Tang, B., Watson, C. W.-M., & Moore., R. C. (2019, July). Ecological momentary assessment of cannabis use in older persons living with HIV: Relationships with sleep and social activity. Oral presentation at the 3rd Annual Scientific Meeting of the Research Society of Marijuana Conference in Vancouver, WA.

3. **Campbell, L. M.,** Fennema-Notestine, C., Saloner, R., Hussain, M., Chen, A., Franklin, D., Umlauf, A., Ellis, R. J., Collier, A. C., Marra, C. M., Clifford, D. B., Gelman, B. B., Sacktor, N., Morgello, S., McCutchan, J. A., Letendre, S., Grant, I., Heaton, R. K. & the CHARTER Group. (2019, February). Use of neuroimaging to inform optimal neurocognitive criteria for detecting HIV-associated brain abnormalities. Oral presentation at the 47th meeting of the International Neuropsychological Society in New York, NY.

4. Saloner R., **Campbell L. M.,** Serrano, V., Montoya, J. L., Pasipanodya E., Paolillo E. W., Franklin, D., Heaton, R. K., Moore, D. J., & the HNRP and CHARTER Groups (2019, February). Neurocognitive SuperAging in older adults living with HIV: Demographic, neuromedical and everyday functioning correlates. Oral presentation at the 47th meeting of the International Neuropsychological Society in New York, NY.

5. **Campbell, L. M.,** Sundermann, E., Letendre, S., Kallianpur, A., Hulgan, T., Montoya, J. L., Ellis, R., Grant, I., Heaton, R.K., Moore, D. J., & Moore, R. C. (2018, September). The relationship between amnestic mild cognitive impairment and biomarkers of inflammation among adults living with HIV. Oral presentation at the 9th International Workshop on HIV & Aging in New York, NY.

6. Saloner, R., Heaton, R. K., **Campbell**, **L. M.,** Chen, A., Franklin, D., Ellis, R. J., Collier, A., Marra, C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., McCutchan, J. A., Letendre, S., Grant, I., Fennema-Notestine, C., & The CHARTER Group (2018, February). Effects of comorbidity burden and age on brain integrity in HIV. Oral presentation at the 9th International Workshop on HIV & Aging in New York, NY.

7. Sanderson-Cimino, M., Eppig, J., Sorg, S., **Campbell, L. M.,** Granholm, E., Kremen, W. S., & Bondi, M. W. (2017, February). The relationship between locus coeruleus integrity and biomarkers of Alzheimer's disease; A magnetic resonance imaging study. Symposium presentation presented at the 45th meeting of the International Neuropsychology Society in New Orleans, LA.

CONFERENCE POSTER PRESENTATIONS

1. Lobo, J.D., Sundermann, E.E., Bondi, M.W., **Campbell, L. M.,** Gouaux, B., Letendre, S., & Moore, D.J. (2023, February). CSF markers of AD-related pathology relate to aMCI and HIV-associated neurocognitive disorder among people with HIV. Accepted for poster presentation at the 51st meeting of the International Neuropsychological Society in San Diego, CA.

2. Kohli, M., **Campbell, L. M.,** Sundermann, E. E., Bondi, M. W., Gilber, P., Franklin, D., Letendre, S., Heaton, R. K., Patel, P. B., Morgello, S., Gelman, B., Clifford, D., Moore, R. C., & Moore, D. J. (2023, February). Examining the independent and additive effects of family history of dementia and apolipoprotein ε4 on neurocognitive performance among people with HIV. Accepted for poster presentation at the 51st meeting of the International Neuropsychological Society in San Diego, CA.

3. **Campbell, L. M.,** Fennema-Notestine, C., Barrett, A., Sundermann, E., Bondi, M. W., Saloner, R., Clifford, D., Ellis, R. J., Franklin, D., Gelman, B., Grant, I., Heaton, R. K., Marra, C., Moore, D. J., Morgello, S., Letendre, S., & Moore, R. C. (2022, February). Prefrontal cortex, not medial temporal lobe, is associated with memory in middle-aged persons with HIV. Poster presented at the virtual 50th meeting of the International Neuropsychological Society in New Orleans, LA.

4. Yu, J., **Campbell, L. M.,** Py, A., Heaton, A., Taylor, R., Masters, M. C., Erlandson, K., Sundermann, E., Waldrop, D. G., Moore, D. J., Torre, P., Salmon, D., Ellis, R., Anderson, A. M., & Moore, R. C. (2022, February). Objectively-measured balance is associated with cognition in older adults with HIV. Poster presented at the virtual 50th meeting of the International Neuropsychological Society in New Orleans, LA.

5. Yu, J., **Campbell, L. M.,** Heaton, A., Kamalyan, L., Marquine, M. J., Zlatar, Z. Z., Moore, D. J., & Moore, R. C. (2021, September). Depression may play larger role in subjective cognitive decline in older adults with HIV than HIV-related stigma. Poster presented at the virtual 12th International Workshop on HIV & Aging.

6. **Campbell, L. M.,** Montoya, J. L., Fazeli, P. L., Marquine, M. J., Ellis, R. J., Jeste, D. V., Moore, D. J., & Moore, R. C. (2021, August). Physical activity and nutrition in persons with HIV: Relationships with health-related quality of life. Poster presented at the 2021 virtual conference for the American Psychological Association.

7. **Campbell, L. M.,** Parrish, E., Heaton, A., Swendsen, J., Depp, C. A., & Moore, R. C. (2021, February). The relationship between contextual factors, performance, and validity of smartphone-based mobile cognitive tests of executive function and learning. Poster presented at the virtual 49th meeting of the International Neuropsychological Society.

8. Fisher, A., **Campbell, L. M.,** Sun-Suslow, N., Kohli, M., Tang, B., Lee, E. E., Heaton, A., & Moore, R. C. (2021, February). Intra-individual variability in objectively-measured sleep

quality is associated with worse cognition in middle-aged and older adults with and without HIV. Poster presented at the virtual 49th meeting of the International Neuropsychological Society.

9. **Campbell, L. M.,** Heaton, A., Sun-Suslow, N., Heaton, R. K., Ellis, R. J., Moore, D. J., & Moore, R. C. (2020, September). Greater fatigue is associated with worse neurocognition in older persons with HIV. Poster presented at the virtual 11th International Workshop on HIV & Aging.

10. Fisher, A., Sun-Suslow, N., **Campbell, L. M.,** Tang, B., Lee, E., & Moore, R. C. (2020, June). An ecological momentary assessment study examining sleep on next-day cognitive abilities in adults with and without HIV. Accepted for poster presentation at the 18th meeting of the American Academy of Clinical Neuropsychology in Washington DC [Conference Cancelled due to COVID-19].

11. **Campbell, L. M.,** Sundermann, E., Letendre, S., Kallianpur, A. R., Hulgan, T., Montoya, J. L., Ellis, R. J., Grant, I., Heaton, R. K., Moore, D. J., & Moore, R. C. (2020, February). Peripheral inflammation is associated with memory decline in older persons living with HIV. Poster presented at the 48th meeting of the International Neuropsychological Society in Denver, CO.

12. Paolillo, E. W., **Campbell, L. M.,** Delgadillo, J. D., Heaton, A., Sundermann, E., Swendsen, J., & Moore, R. C. (2020, February). Mood predicts performance on repeatedly administered mobile cognitive tests among older adults living with and without HIV. Poster presented at the 48th meeting of the International Neuropsychological Society in Denver, CO.

13. Serrano, V., Montoya, J. L., **Campbell, L. M.,** Sundermann, E., Heaton, R. K., & Moore, D. J. (2019, October). The relationship between vascular endothelial growth factor (VEGF) and amnestic mild cognitive impairment among older adults living with HIV. Poster presented at the Society for Neuroscience at Chicago, IL.

14. Pope, C., Yang, J., Kamalyan, L., **Campbell, L. M.,** Heaton, A., Marquine, M., & Moore, R. C. (2019, July). Digital assessment of life-space and its associations with frailty, physical activity, and HIV serostatus in older adults. Poster presented at the 3rd annual Sustained Training in Aging and HIV Research Workshop at UC San Diego.

15. Balon, E., Sun-Suslow, N., Montoya, J. L., Saloner, R., **Campbell, L. M.,** Serrano, V., Ellis, R., & Moore, D. J. (2019, October). Increased frailty symptoms relate to poorer self-reported sleep quality among older people living with HIV. Poster presented at the 10th International Workshop on HIV & Aging in New York, NY.

16. **Campbell, L. M.,** Kohli, M., Heaton, A., Higgins, H., Lee, E., Kaufmann, C. N., Heaton, R. K., Moore, D. J., & Moore, R. C. (2019, October). Objective and subjective sleep measures are associated with neurocognition in middle-aged and older adults with and without HIV. Poster presented at the 39th National Academy of Neuropsychology conference in San Diego, CA.

17. Kamarsu, S., **Campbell, L. M.,** Paolillo, E. W., Filip, T. F., Swendsen, J., Depp. C., & Moore, R. C. (2019, October). Greater time spent watching TV is related to worse real-time cognitive performance in older adults with and without HIV. Poster presented at the 39th National Academy of Neuropsychology conference in San Diego, CA.

18. **Campbell, L. M.,** Delgadillo, J. D., Paolillo, E. W., Sundermann, E. E., Holden, J., Schweitzer, P., Swendsen, J., & Moore, R. C. (2019, July). Mobile monitoring of cognition in middle-aged and older adults with and without amnestic mild cognitive impairment: Implications for Alzheimer's disease clinical trials. Poster presented at the 2019 Alzheimer's Association International Conference in Los Angeles, CA.

19. Moore, R. C., **Campbell, L. M.,** Delgadillo, J., Heaton, A., Leow, A. D., & Swendsen, J. (2019, May). Digital cognitive assessment in psychiatry research. Poster presented at 74th Annual Society for Behavioural Psychiatry in Chicago, IL.

20. Osuna, J., Mestre, Z., Thomas, K. R., Hays, C., **Campbell, L. M.,** & Wierenga, C. E. (2019, February). The relationship between arterial stiffness, APOE genotype, and cognition in cognitively normal older adults. Poster presented at the 47th meeting of the International Neuropsychological Society in New York, NY.

21. Paolillo, E. W., Saloner, R., Montoya, J. L., **Campbell, L. M.,** Pasipanodya, E., Iudicello, J. E., Moore, R. C., & Moore, D. J. (2018, November) Combined effects of HIV and past methamphetamine use disorder on frailty, neurocognition, and everyday functioning. Poster presented at the 38th National Academy of Neuropsychology conference in New Orleans, LA.

22. Delgadillo, D. J., **Campbell, L. C.,** Heaton, A., Rooney, A. S., Serrano, V., Marquine, M. J., Jeste, D. V., Moore, D. J., & Moore, R. C. (2018, April). The association of clinic-demographics and positive psychological factors with religiosity/spirituality among persons living with HIV. Poster presented at the 2018 Western Psychological Association conference in Portland, OR.

23. Zlatar Z. Z., Hays, C. C., Mestre, Z., **Campbell, L. M.,** Meloy, M. J., Bangen, K. J., Kerr, J., & Wierenga, C. E. (2018, March). Relationships between accelerometer-measured sedentary time and physical activity with resting cerebral blood flow in aging. Poster presented at 3rd Okanagan Cardiovascular and Respiratory Symposium in British Colombia.

24. **Campbell, L. M.,** Eppig, J., Thomas, K., Edmonds, E. C., & Bondi, M. W. (2018, February) Cognitive performance and Alzheimer's disease biomarkers in SuperAging and normal older adults. Poster presented at the 46th meeting of the International Neuropsychology Society in Washington DC.

25. Osuna, J. R., Zlatar, Z. Z., Hays, C. C., **Campbell, L. M.,** & Wierenga, C. E. (2018, February) The benefits of moderate-intensity physical activity on cognition in older adults.

Poster presentation at the 46th meeting of the International Neuropsychology Society in Washington DC.

26. Sorg, S. F., Clark, A. L., **Campbell, L. M.,** Werhane, M., Holiday, K., Merritt, V., Jak, A. J., Schiehser, D. M., & Delano-Wood, L. (2018, February) Subjective ratings of retrospective and prospective memory difficulties in veterans with mild traumatic brain injury. Poster presented at the 46th meeting of the International Neuropsychology Society in Washington DC.

27. **Campbell, L. M.,** Hays, C. C., Zlatar, Z. Z., Meloy, M. J., & Wierenga, C.E. (2017, February). Relationship between cerebral blood blow and famous face naming in cognitively normal older adults. Poster presented at the 45th meeting of the International Neuropsychology Society in New Orleans, LA.

28. Eppig, J., Nation, D. A., Meier, I., Brickman, A. M., **Campbell, L. M.,** Sanderson-Cimino, M., Bangen, K. J., Delano-Wood, L., & Bondi, M. W. (2017, February). APOE-ε4 moderates the relationship between lobar microbleeds and a diagnosis of mild cognitive impairment. Poster presented at the 45th meeting of the International Neuropsychology Society in New Orleans, LA.

29. Hays, C. C., Zlatar, Z. Z., **Campbell, L. M.,** Meloy, M. J., & Wierenga, C. E. (2017, February). Relationship between pulse wave velocity, cerebral blood flow, and memory in cognitively normal older adults. Poster presented at the 45th meeting of the International Neuropsychology Society in New Orleans, LA.

30. Hays, C. C., Zlatar, Z. Z., **Campbell, L. M.,** Meloy, M. J., & Wierenga, C. E. (2017, February). Subjective cognitive decline modifies the relationship between cerebral blood flow and memory function in cognitively normal older adults. Poster presented at the 45th meeting of the International Neuropsychology Society in New Orleans, LA.

31. Zlatar, Z. Z., Hays, C. C., **Campbell, L. M.,** Bangen, K. J., Meloy, M. J., & Wierenga, C. E. (2017, February). Moderate physical activity is associated with higher brain perfusion whereas sedentary time is related to lower perfusion: Associations with cognition in older adults. Poster presented at the 45th meeting of the International Neuropsychology Society in New Orleans, LA.

32. **Campbell, L. M.,** Eppig J., Edmonds, E. C., Wierenga, C. E., Delano-Wood, L., Jak, A. J., & Bondi, M. W. (2016, February). Comparisons of traditional and comprehensive approaches in defining SuperAgers. Poster presented at the 44th meeting of the International Neuropsychological Society meeting in Boston, MA.

33. Eppig, J. Edmonds, E. C., **Campbell, L. M.,** Sanderson-Cimino, M., Delano-Wood, L., & Bondi, M. W. (2016, February). Statistically-derived subtypes in MCI: A latent profile analysis. Poster presented at the 44th meeting of the International Neuropsychological Society meeting in Boston, MA.

34. Hays, C., Zlatar, Z. Z., Bischoff-Grethe, A., **Campbell, L. M.,** Meloy, M. J., Galasko, D., & Wierenga, C. E. (2016, February). Relationship between cerebral blood flow and cerebrospinal fluid levels of amyloid beta and tau in normal cognitive aging. Poster presented at the 44th meeting of the International Neuropsychological Society meeting in Boston, MA.

35. Zlatar, Z. Z., Bischoff-Grethe, A., Hays, C., **Campbell, L. M.,** Meloy, M. J., & Wierenga, C. E. (2016, February). Interactive effects of APOE genotype and cognition on brain perfusion in normal aging and mild cognitive impairment. Poster presented at the 44th meeting of the International Neuropsychological Society meeting in Boston, MA.

36. **Campbell, L.,** Eppig, J., Edmonds, E. C., Delano-Wood, L., Jak, A. J., Sanderson-Cimino, M., Bondi, M. W. (2015, February). The relationship between SuperAging and APOE genotype, vascular risk, and brain morphology. Poster presented at the 43rd meeting of the International Neuropsychological Society meeting in Denver, CO.

37. Eppig. J., **Campbell, L. M.,** Edmonds, E. C., Jak, A. J., Delano-Wood, L., Sanderson-Cimino, M., & Bondi, M. W. (2015, February). Superior verbal memory in SuperAgers: Generalizability to learning, visual memory, language, and executive functioning. Poster presented at the 43rd meeting of the International Neuropsychological Society meeting in Denver, CO.

38. Sanderson-Cimino, M., Delano-Wood, L., Clark, A. L., Luc, N., Eppig, J., **Campbell, L. M.,** Jak, A. J., & Bondi, M. W. (2015, February). Age moderates the effect of elevated pulse pressure on white matter lesion burden in older adults. Poster presented at the 43rd meeting of the International Neuropsychological Society meeting in Denver, CO.

ABSTRACT OF THE DISSERTATION

Assessing brain morphology and inflammation in relation to episodic memory profiles among aging adults with HIV

by

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Rationale: Identifying persons with HIV (PWH) at risk for Alzheimer's disease (AD) is complicated because memory deficits are common in HIV-associated neurocognitive disorders (HAND) and amnestic mild cognitive impairment (aMCI; a precursor to AD). Due to differences in underlying brain changes, recognition deficits are common in aMCI but not in HAND; therefore, recognition may be a useful neurocognitive marker to differentiate these etiologies. There is a paucity of research aimed at identifying PWH on an AD trajectory and understanding biological mechanisms that may put PWH at higher risk of aMCI/AD. This study examined the relationship between baseline brain integrity and memory (i.e., recall and recognition) and the

relationship between inflammation, brain integrity, and memory.

Design: This study utilized longitudinal data from the CNS HIV Antiretroviral Therapy Effects Research program from 92 PWH between ages 45-68. Aim 1 used multivariable linear regression and logistic regression to examine neuroanatomical correlates of memory. Aim 2 utilized multilevel modeling to examine if baseline structural neuroimaging predicts memory decline (average follow-up = 5.7 visits over 6.5 years). Aim 3 examined if medial temporal lobe (MTL) structures mediate the association between peripheral inflammatory biomarkers (i.e., IL-6, TNF-a, CCL2, CRP, CXCL10) and memory.

Results: Thinner pars opercularis thickness was associated with impaired recognition (p=0.012) and worse delayed recall (p=0.001), and thinner rostral middle frontal thickness was associated with worse delayed recall (p=0.006). Memory was not associated with MTL, basal ganglia, primary motor cortex, or other prefrontal structures. In Aim 2, recognition impairment was variable over time, and there was little decline in delayed recall (i.e., T-score change of -0.041 per year). Baseline MTL integrity was not associated with memory decline (ps>0.40). Lastly, MTL structures did not mediate the association between inflammatory biomarkers and memory.

Conclusions: Memory in this sample of middle-aged PWH was associated with prefrontal structures and not MTL structures. MTL structures did not predict memory decline. This may suggest that memory is more related to frontally mediated etiologies, such as HIV, rather than AD pathology in middle-aged PWH. Additional research is needed to clarify if recognition can be used clinically to differentiate aMCI and HAND.

1. INTRODUCTION

Due to the advent of antiretroviral therapy (ART) in the mid-1990s, HIV is now considered a chronic medical condition rather than a devastating terminal illness. Life expectancy for persons living with HIV (PWH) is now similar to the general population (Samji et al., 2013). Currently, over 50% of PWH (i.e., over 485,000) in the United States are over the age of 50, with aging trends projected to continue (Centers for Disease Control and Prevention, 2018). As such, researching aging with HIV is critical to better understand the impact of HIV on the aging process and how it may differ from the general population.

Aging with HIV is associated with an increased risk of HIV-associated neurocognitive disorders (HAND; Cherner et al., 2004; Valcour et al., 2004; Wing, 2016), the current research term to describe neurocognitive impairments associated with HIV disease, with some evidence of accelerated brain aging (Cole et al., 2017; Pathai et al., 2013; Sheppard et al., 2017). Given the potentially compounding effects of HIV and aging on the brain, the rapidly growing population of aging PWH may be at increased risk for Alzheimer's disease (AD) and its precursor, amnestic mild cognitive impairment (aMCI; Cohen et al., 2015; Milanini & Valcour, 2017; Rubin et al., 2019b). As such, there is an urgent public health need to identify clinical tools to accurately identify older PWH on the AD trajectory and understand biological mechanisms that may put PWH at higher risk of aMCI/AD. To clarify, in the HIV literature, "older" PWH usually refers to PWH aged 50 and over; however, in the aging literature, "older" usually refers to people aged 65 and older, and "middle-age" refers to people aged 45 to 64. To rectify this discrepancy in terminology, the aging literature terminology will be used when discussing both the HIV literature and the aging literature.

HAND remains prevalent in the ART era (20-50%; Heaton et al., 2010; Saloner & Cysique, 2017). While the pathogenesis of HAND is not entirely clear, HAND is thought to be the result of the neurotoxic cascade initiated by HIV (Saylor et al., 2016). The majority of neurocognitive deficits associated with HAND are in the mild range and do not significantly impact everyday functioning (i.e., asymptomatic neurocognitive impairment per the Frascati criteria; (Heaton et al., 2010), and executive functioning, learning, and memory (specifically delayed recall) deficits are most common (Heaton et al., 2011). Importantly, longitudinal studies have shown that HAND is usually non-progressive (Clifford & Ances, 2013).

AD is a neurodegenerative disease associated with progressive cognitive and functional impairment (Alzheimer's Association, 2017). AD is the most common cause of dementia, and it affects 10% of persons without HIV over the age of 65 and 17% between the ages of 75-84 (Alzheimer's Association, 2017). AD is characterized by the accumulation amyloid plaques ($A\beta_{42}$) and tau tangles in the brain, that start in the medial temporal lobe (MTL) and result in initial atrophy of the medial temporal lobe and later more widespread atrophy (Alzheimer's Association, 2017; Jack et al., 2018). These brain changes start years to decades before clinical symptoms appear (Ritchie et al., 2015; Sutphen et al., 2015; Villemagne et al., 2011).

On neuropsychological testing, AD typically presents initially with impairment in memory, which progresses to global impairment and loss of independent functioning (Smith, 2016). Mild cognitive impairment (MCI) is defined as the transitional stage between cognitively normal and major neurocognitive impairment (i.e., dementia) in which persons have observable cognitive deficits but these deficits are not yet significantly impacting everyday functioning. MCI can be further divided into amnestic (i.e., aMCI) and non-amnestic MCI subtypes, with aMCI being more associated with AD (Bondi & Smith, 2014). While participants are often

dichotomized as “MCI” or “cognitively unimpaired,” cognitive decline associated with AD is insidious; therefore, even milder deficits in memory in participants classified as cognitively unimpaired are associated with underlying AD pathology (Hedden et al., 2013) such as amyloid accumulation or medial temporal lobe atrophy (Thomas et al., 2020).

1.1 Importance of Discerning HAND from aMCI in People with HIV

Due to the overlap in cognitive presentation (i.e., memory impairments), middle-aged and older PWH are at risk of erroneously being classified as HAND, due to HIV diagnosis, when they may instead be on an AD trajectory. Given that aMCI is associated with progressive cognitive and functional impairment, as opposed to HAND, which is more stable, it is imperative that the etiology of the cognitive impairment is correctly identified (see Figure 1). While there is currently no cure for AD, a misdiagnosis of HAND when a person with HIV has aMCI limits the opportunity for early intervention when interventions may be most beneficial (Sperling et al., 2011). For example, early identification of AD allows more time for life planning and the acquisition of compensation strategies, which may prolong independent functioning, and, by extension, sustain quality of life (Sherman et al., 2017). Furthermore, accurate diagnosis is important to allay concerns in PWH without indication of an AD trajectory.

It is hypothesized that PWH may be at increased risk of AD due to the compounding effects of HIV and aging on the brain (i.e., decreased brain reserve), chronic inflammation despite viral suppression, increased prevalence of vascular and metabolic risk factors (i.e., type 2 diabetes, hypertension), and potentially common pathophysiological pathways (Cohen et al., 2015; Milanini & Valcour, 2017; Rubin et al., 2019b). While little work has been done in this space, several recent case reports on AD in PWH have highlighted the risk of delayed diagnosis,

detailed complications determining the etiology of cognitive impairment, and underscored the clinical need for tools to differentiate HAND and aMCI (Calcagno et al., 2021; Hellmuth et al., 2018; Makitalo et al., 2015; Morgello et al., 2018; Turner et al., 2016).

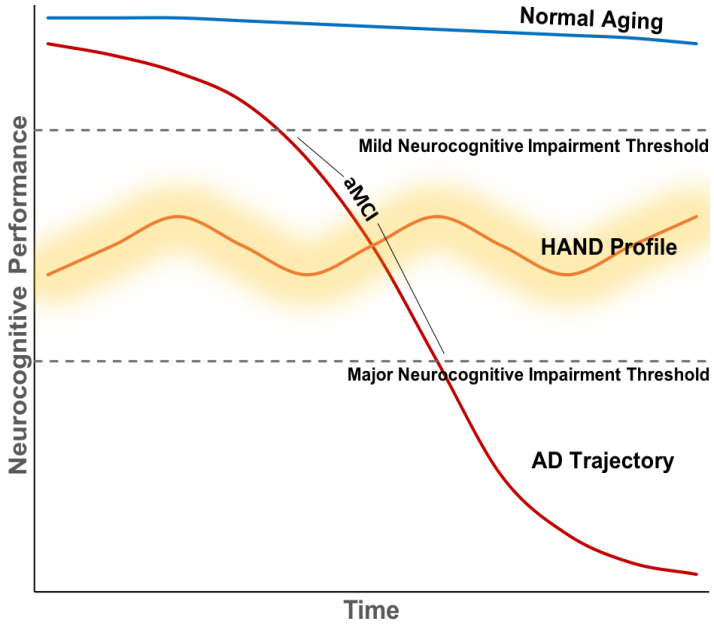

Figure 1. HAND vs. aMCI trajectories
Note. The blue line depicts the normal aging, in which there may be some decline but do not meet criteria for mild neurocognitive disorder. The yellow line depicts the HAND trajectory in which there may be some fluctuation, but it does not usually progress to major neurocognitive impairment. The red line depicts the AD trajectory, in which a person on this trajectory would first be classified as "aMCI" and then decline to major neurocognitive impairment (i.e., dementia).

Additionally, there is some evidence from the HIV and aging literature to suggest that memory may be particularly affected in older PWH; however, most of these studies do not consider other etiologies that may be contributing to the observed findings. For example, Goodkin et al. (2017) found that there was a greater than expected effect of aging on episodic memory in PWH aged 50 and over, and Seider et al. (2014) found that verbal memory declines more rapidly with age in PWH as compared to HIV-negative comparison participants. Moreover,

in a recent study using latent class analysis to examine a group of PWH aged 50 and over, we found that three classes emerged: a multidomain impaired group, a learning and memory impaired group, and a cognitively unimpaired group (Pasipanodya et al., 2021).

1.2 Similarities and Differences in aMCI and HAND: The Clinical Utility of Neuropsychological Profiles in Differential Diagnosis

Due to the medial temporal lobe involvement in aMCI, the cognitive profile is described as "amnestic", with encoding, storage, and rapid forgetting deficits observed as poor learning, recall, *and* recognition on memory tests (Smith & Bondi, 2013). Conversely, HIV particularly impacts fronto-striatal systems (i.e., basal ganglia and prefrontal structures), and the fronto-striatal involvement associated with HAND accounts for a "subcortical" cognitive presentation. Thus, memory deficits in HAND are characterized by relatively normal memory storage and retention but impaired encoding and retrieval resulting in poor learning and delayed recall, but intact recognition (i.e., ability to recognize previously learned information upon repeated presentation; Becker et al., 1995; Peavy et al., 1994; Scott et al., 2011; White et al., 1997). This "subcortical" presentation in HAND has been observed even as PWH age (Scott et al., 2011). Therefore, recognition may be more indicative of aMCI than HAND and a useful tool for differential diagnosis (see Table 1). However, because recognition has historically been spared in HAND and only recently have PWH been reaching the ages at which they may develop aMCI/AD, there is little research examining recognition deficits in the context of HIV.

Of note, deficits in other domains are unlikely to aid in differential diagnosis without further research. For example, while aMCI is characterized by memory deficits, other deficits, such as executive dysfunction, are also quite common in aMCI and AD (Edmonds et al., 2015;

Kirova et al., 2015). Therefore, the presence of executive functioning deficits, which are common in HAND, could be indicative of HAND, aMCI, or a mixed HAND and aMCI profile. Moreover, biomarkers (e.g., $A\beta_{42}$) may aid in differential diagnosis in the future; however, elevated amyloid beta is observed in HIV (Ortega & Ances, 2014), so more research is needed in order for biomarkers to be beneficial in differential diagnosis of HAND and aMCI.

Table 1. Summary table of similarities and differences between HIV and aMCI/AD

	HIV	**aMCI/early AD**
Memory	Impaired delayed recall, intact recognition	Impaired delayed recall and recognition
$A\beta_{42}$	Inconsistently increased	Very increased
p-tau	Inconsistently increased	Increased
Neuroimaging	Changes in basal ganglia and prefrontal cortex	Changes in the medial temporal lobe
Inflammation	Increased	Increased

1.3 Emerging Evidence that Recognition Deficits in Persons with HIV are Associated with $A\beta_{42}$ Plaques

Our research group at the HIV Neurobehavioral Research Program (HNRP) has begun to examine neuropsychological methods to identify aMCI among PWH using adapted Jak/Bondi MCI criteria. Jak/Bondi MCI criteria is an empirically based MCI criteria that has been shown to have greater associations with AD biomarkers and identify more participants who progress to dementia than traditional MCI diagnostic approaches (Bondi et al., 2014; Jak et al., 2009). Our group utilized the basis of the Jak/Bondi criteria and adapted it to capitalize on the neuropsychological differences between HAND and aMCI (i.e., recognition impairment; (Sundermann et al., 2021a). Thus, aMCI was defined as impairment (i.e., >1.0 SD below

demographically corrected normative mean) on at least two memory tests with the adaptation that at least one impaired test be a test of recognition.

In a sample of 80 PWH from the National NeuroAIDS Tissue Consortium with neuropathologically characterized $A\beta_{42}$ and neuropsychological testing within a year of death, 40 participants met the adapted criteria for aMCI. Twenty-nine of the participants with aMCI (73%) were also classified with HAND. The aMCI group was 3.5 times more likely to have the presence of $A\beta_{42}$ plaques. Conversely, when the same sample was split into HAND and no HAND groups, the presence of $A\beta_{42}$ plaques was not significantly associated with the HAND group. In sum, these findings provide preliminary data to further support that aMCI may go undetected in a large proportion of PWH with HAND, and these PWH may be misclassified or have a mixed HAND and aMCI profile. Secondly, these preliminary analyses also suggest that recognition deficits in older PWH are sensitive to AD pathology (Sundermann et al., 2021a).

1.4 Neuroimaging in aMCI/AD and HIV

Magnetic resonance imaging (MRI) has shed light on brain changes associated with aMCI and AD and is increasingly used in clinical assessment of suspected AD (Frisoni et al., 2010). Medial temporal lobe atrophy (i.e., particularly the hippocampus and entorhinal cortex) is a core feature of aMCI/AD and has been shown to correlate with disease progression (i.e., both cognition and AD pathology; Pini et al., 2016) and predict progression from cognitively normal to aMCI (Bangen et al., 2018). However, AD is also associated with more widespread cortical and subcortical atrophy and white matter abnormalities, particularly as the disease progresses (Pini et al., 2016). While neuroimaging has been used extensively to study aging and AD, most

of these neuroimaging studies exclude PWH (e.g., Alzheimer's Disease Neuroimaging Initiative). Consequently, it is unclear if aging/AD research is generalizable to older PWH.

HIV has historically been associated with early changes to fronto-striatal circuits (i.e., basal ganglia and prefrontal regions), although recent neuroimaging studies also report cortical atrophy (Clifford et al., 2017; Holt et al., 2012; Masters & Ances, 2014; O'Connor et al., 2018). Similarly, HAND has been associated with fronto-striatal circuits, and, in more recent years, has also been associated with more cortical structures (Alakkas et al., 2019; Ances & Hammoud, 2014; Nichols et al., 2019). Neuroimaging studies have examined neuroanatomical correlates of delayed recall as well as the effect of age on the brain within the context of HIV (Maki et al., 2009; Milanini et al., 2019; Pfefferbaum et al., 2014; Wang et al., 2015).

Studies comparing PWH with HAND and HIV-negative participants with MCI or AD have shown that hippocampal volumes were able to discern HAND and MCI/AD (Milanini et al., 2019; Zhang et al., 2016). Additionally, within the context of HIV, decline in memory has been associated with hippocampal atrophy (Pfefferbaum et al., 2014; Wang et al., 2015). However, there are notable limitations to the current literature. For example, most studies have been couched in the context of HAND, are not aimed at examining aMCI within the context of HIV, nor do they consider other etiologies (Holt et al., 2012; Kuhn et al., 2018). Additionally, several neuroimaging studies examining the effect of aging in PWH have samples with mean ages in the late 30s or early 40s, which is likely before the initiation of AD pathology (Braak et al., 1996). Moreover, memory recognition, which could improve differentiation of HAND and aMCI, was not examined in these studies.

1.5 Inflammation: A Risk Factor Shared by HAND and AD

Both HIV and aMCI are associated with chronic, low-grade inflammation (Hong & Banks, 2015; McGeer & McGeer, 2010). As such, inflammation may be one biological mechanism that puts PWH at greater risk of aMCI. Peripheral inflammatory markers can cross the blood-brain barrier, and there is mounting evidence to support the hypothesis that chronic inflammation exacerbates both $A\beta_{42}$ and p-tau pathology and plays a role in the pathogenesis of AD (Kinney et al., 2018; McGeer & McGeer, 2010; McGeer et al., 2016). There is ample evidence linking increased inflammation (e.g., IL-6, TNF-α, CCL2, CRP, CXCL10) to brain atrophy, cognition, and cognitive decline in late life (Bettcher et al., 2012; Jefferson et al., 2007; Satizabal et al., 2012; Shen et al., 2019), with emerging evidence that this link is present even in midlife (Marsland et al., 2015; Walker et al., 2019).

Chronic inflammation is also present in PWH despite viral suppression (Hong & Banks, 2015; Neuhaus et al., 2010; Wada et al., 2015), and is hypothesized to contribute to and exacerbate HAND (Gannon et al., 2011). Due to this overlap, inflammation may be one factor that also puts PWH at greater risk of aMCI/AD. While the literature has highlighted the need to investigate this association, little research currently exists (Cohen et al., 2015; Milanini & Valcour, 2017; Rubin et al., 2019b). Determining how inflammation impacts brain integrity and cognition in middle-aged PWH could have great implications for our overall understanding of the role of inflammation in AD and for the development of early intervention strategies to lower the risk of AD within PWH.

I have begun to examine the relationship between inflammation and change in memory. These preliminary analyses included 57 PWH aged 50 and older (mean age=56) with peripheral inflammatory markers (i.e., TNF-α, CCL-2, and IL-6) and neuropsychological testing at baseline

and at 1-year follow-up. Overall, I found that baseline concentrations of inflammatory biomarkers were not associated with baseline memory performance. However, using multivariable linear regressions, IL-6 (β=-0.286, *p*=0.043) and TNF-α (β=-0.282, *p*=0.043) were associated with decline in delayed recall, and greater baseline concentrations of CCL2 were associated with decline in recognition (β= -0.349, *p*= 0.019). These inflammatory markers were not significantly associated with change in any other cognitive domain. Overall, these findings support the hypothesis that inflammatory markers may be related to cognitive changes associated with abnormal memory decline (Campbell, *under review*).

As AD drug trials targeting amyloid continue to fail, there is increased focus on repositioning current drugs, such as anti-inflammatory drugs, to reduce the risk of AD (Bachurin et al., 2017; Graham et al., 2017). Epidemiological studies have shown that persons taking anti-inflammatory drugs for diseases such as rheumatoid arthritis had a reduced risk of developing AD (Kinney et al., 2018). Moreover, small, randomized control trials examining anti-inflammatory drugs such as TNF-α inhibitors (i.e., etanercept), though preliminary, have yielded encouraging results (Butchart et al., 2015; Tobinick, 2007). If larger studies show that anti-inflammatory drugs can lower the risk of AD, PWH may particularly benefit.

1.6 Middle Age: The Critical Time to Identify Those at Highest Risk of AD

Brain changes (i.e., AD pathology and medial temporal lobe atrophy) associated with future cognitive decline are evident in midlife, several years before cognitive impairment in aMCI and AD (Ritchie et al., 2015; Sutphen et al., 2015; Villemagne et al., 2011). Additionally, longitudinal research studies have shown that more subtle differences in episodic memory in midlife (e.g., worse memory performance than "non-decliners" but not necessarily in the

"impaired" range) is associated with a decline in memory years later (Clark et al., 2016; Kremen et al., 2014; Okonkwo et al., 2014; Singh-Manoux et al., 2012). Additionally, Jak et al. (2015) found that midlife memory performance is associated with hippocampal atrophy. As a result, there has been a shift in the aging field to characterize and identify middle-aged adults in the preclinical phase of AD rather than primarily focusing on elderly cohorts in which symptoms and pathology are already present (Sperling et al., 2011). Furthermore, there is a growing literature suggesting that midlife risk factors (e.g., hypertension, type 2 diabetes mellitus, obesity, lower physical activity) are associated with future cognitive decline, suggesting that midlife may be a critical time point when some interventions may be efficacious in augmenting cognitive trajectories (Bangen et al., 2013; Rovio et al., 2005; Schubert et al., 2019; Whitmer et al., 2005).

In the HIV literature, most aging research has focused on PWH in midlife. The majority of older PWH are currently between the ages of 50 to 65, with a much smaller percentage over the age of 65. However, aging trends in the HIV population are predicted to continue (Centers for Disease Control and Prevention, 2018). Additionally, age-associated physical comorbidities (e.g., cardiovascular disease, frailty) appear 5-10 years earlier in PWH (Deeks & Phillips, 2009; Greene et al., 2015; Guaraldi et al., 2011), and, there is evidence of premature brain aging (Cole et al., 2017; Horvath & Levine, 2015; Kuhn et al., 2018). Due to the neurotoxic effects of HIV and ART, as well as medical comorbidities and possible accelerated brain aging, PWH also may have less brain reserve to compensate for accumulating neurodegenerative pathology. Therefore, cognitive deficits indicative of aMCI could appear earlier in PWH compared to HIV-negative peers. Taken together, examining PWH in mid-life is advantageous as it could identify those with early signs of aMCI when interventions may be particularly efficacious.

1.7 Specific Aims and Hypotheses

This project aims to fill critical gaps in the literature by investigating the relationship between brain integrity and memory (i.e., delayed recall *and* recognition) in aging (i.e., aged 45-68) PWH and further examining the role of inflammation. The aims of this study are:

Aim 1. To examine the neuroanatomical correlates (i.e., three regions of interest: the medial temporal lobe, basal ganglia, and prefrontal cortex) of delayed recall and recognition in aging persons with HIV using structural neuroimaging data.

Aim 1a. To examine the relationship between recognition memory and three regions of interest. ***Hypothesis 1a:*** Recognition memory accuracy will be most strongly related to medial temporal lobe structures. Recognition may be associated with basal ganglia and prefrontal cortex structures, but less so than medial temporal lobe structures.

Aim 1b: To examine the relationship between delayed recall and the three regions of interest. ***Hypothesis 1b:*** Delayed recall will be associated with medial temporal lobe structures as well as fronto-striatal circuit structures (i.e., basal ganglia and prefrontal cortex).

Aim 1c: To further validate the specificity of recognition-medial temporal lobe relationships, processing speed and psychomotor skills, which should be less associated with medial temporal lobe structures (Paul et al., 2008; Wright et al., 2016), will also be examined. ***Hypothesis 1c:*** Processing speed and psychomotor skills will be more strongly associated with basal ganglia and prefrontal cortex structures as compared to medial temporal lobe structures.

Aim 1d: To complete double dissociation and demonstrate that delayed recall and recognition is not related to brain integrity in general, the relationship between delayed recall and recognition and primary motor cortex will also be examined. Given that the primary motor cortex is spared in AD and not found to be associated with memory (Singh et al. 2006), delayed

recall and recognition should be less associated with primary motor cortex structure. ***Hypothesis 1d:*** Recognition and delayed recall will not be significantly associated with the primary motor cortex.

Aim 2: To examine if baseline structural neuroimaging helps to predict amnestic decline. ***Hypothesis 2:*** Smaller baseline medial temporal lobe structures will be associated with decline in both recognition and delayed recall.

Aim 3: To examine if peripheral inflammation is associated with brain structure, and whether brain structure mediates the role between inflammation and memory. ***Hypothesis 3:*** Medial temporal lobe structures will mediate the association between peripheral inflammatory biomarkers and memory decline (i.e., recognition and delayed recall).

2. METHODS

The study retrospectively analyzed de-identified longitudinal data from individuals enrolled in the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) program. In accordance with CHARTER policy, this project received formal approval to use the neuroimaging and longitudinal data for this study.

2.1 Participants

After excluding participants that did not meet inclusion/exclusion criteria as detailed below, the study included 92 PWH between the ages of 45 to 68 years old. All participants underwent at least one structural MRI scan between 2008 and 2010, comprehensive neuropsychological, neuromedical, and neuropsychiatric evaluation, as well as a blood draw. Most participants (n=91) completed at least one follow-up neuropsychological, neuromedical, and neuropsychiatric study visit occurring in 6-month intervals. Participants were drawn from five participating sites: Johns Hopkins University, Mt. Sinai School of Medicine, University of California San Diego, University of Texas Medical Branch, and University of Washington. All CHARTER study procedures were approved by local Institutional Review Boards, and all participants provided written informed consent. UC San Diego IRB approval was sought for the current study, and it was determined by the IRB that this study was exempt.

2.2 Participant Characterization and Inclusion/Exclusion Criteria

The CHARTER study aimed to recruit PWH to reflect the geographic and sociodemographic diversity of PWH around university-affiliated treatment centers in the U.S.; thus, CHARTER inclusion criteria were minimal and did not exclude participants with comorbid

conditions that may impact cognitive function. To determine the extent to which non-HIV-related comorbidities have contributed to neurocognitive impairment, developmental and medical histories of each participant were determined by Dr. R. K. Heaton and re-reviewed by an independent CHARTER clinician investigator. Participants with severe "confounding" comorbidities, as defined by Frascati criteria (i.e., current HAND nosology; Antinori et al., 2007; Heaton et al., 2010), were excluded from this project. Severe "confounding" comorbid conditions include comorbidities that could sufficiently explain neurocognitive deficits and thus preclude a HAND diagnosis. During clinician review, time course of comorbidities in relation to HIV and cognitive decline as well as the severity of comorbidities were considered when making comorbidity classification determination. Comorbid conditions that were reviewed and considered include history of neurodevelopmental disorders (e.g., severe learning disability), cerebrovascular events (e.g., stroke), systemic medical comorbidities (e.g., diabetes, myocardial infarctions, HCV), non-HIV neurological conditions (e.g., traumatic brain injury, seizure disorders), and substance-related comorbidities (Heaton et al., 2010).

This comorbidity classification system has been shown to have excellent inter-rater reliability (Heaton et al., 2010). The decision to exclude confounding comorbidities was further supported by a recent CHARTER paper showing that those with severe "confounding" comorbidities had worse brain integrity, but those with moderate comorbidities (i.e., "contributing" comorbidities) had fairly equivalent brain abnormalities as those with mild comorbidities (i.e., "incidental" comorbidities; Saloner et al., 2019).

Additionally, CHARTER recruited a wide range of ages. To study the effect of aging with HIV, the age range for the current study was restricted to participants that were aged 45 or

older at the time of the MRI scan. Additionally, one participant was excluded from the study given that their T1 structural MRI scan did not yield usable data (e.g., did not properly segment).

2.3 Neuropsychological Evaluation

At each study visit, participants completed a standardized battery of neurocognitive tests. Prior to neuropsychological testing, participants were administered and passed the Hiscock Digit Memory Test, which is a free-standing performance validity test (Hiscock & Hiscock, 1989; Woods et al., 2003). The test battery assessed seven cognitive domains commonly affected by HIV: verbal fluency, executive functioning, processing speed, learning, delayed recall, attention/working memory, and motor skills (Heaton et al., 2010). See Table 2 for a list of neuropsychological tests that were examined in the current study.

Table 2. Neurocognitive tests by domain

Domain	Individual Measures
Delayed recall	Delayed Recall Trials of: Hopkins Verbal Learning Test-Revised (HVLT-R) Brief Visuospatial Memory Test-Revised (BVMT-R)
Recognition	Recognition Trials of: Hopkins Verbal Learning Test-Revised Brief Visuospatial Memory Test-Revised
Processing speed	WAIS-III Digit Symbol WAIS-III Symbol Search Trail Making Test, Part A Stroop Color Trial
Psychomotor skills	Grooved Pegboard Test (dominant & non-dominant hands)
Premorbid Verbal IQ	Wide-Range Achievement Test-III Reading Subtest

Notes. WAIS III = Wechsler Adult Intelligence Scale 3rd Edition

Tests of memory in the CHARTER study included the Hopkins Verbal Learning Test – Revised (HVLT-R; Brandt & Benedict, 2001) and the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997). The HVLT-R and the BVMT-R include three learning trials, a long-delay free recall trial (20 minutes for the HVLT-R and 25 minutes for the BVMT-R) in which participants are asked to recall the stimuli previously presented, and a recognition trial in which participants are presented both target stimuli and non-target stimuli and asked if stimuli were presented in the learning trials. The delayed recall raw score is the total number of words correctly recalled during the long-delay free-recall trial. A recognition discrimination raw score was calculated by subtracting false positives from the total number of true positives. Note, this score is reflective of recognition discriminability, but this will be referred to simply as "recognition" throughout the text. Both the HVLT-R and BVMT-R have six alternate forms to attempt to correct for practice effects.

Raw recognition scores were converted to Z-scores (M=0, SD=1) that account for demographic variables (i.e., age, sex, education, and race/ethnicity) using normative data from the HNRP (Cysique et al., 2011; Heaton et al., 2004; Heaton et al., 2003; Norman et al., 2011). Given that practice effect correction was not available for recognition and participants had a varying number of previous administrations, number of prior neuropsychological evaluations was included as a covariate in statistical analyses examining recognition. Raw delayed recall scores were converted to T-scores (M=50, SD=10) that account for demographic variables (i.e., age, sex, education, and race/ethnicity) and practice effects using normative data from the HNRP. HVLT-R and BVMT-R recognition Z-scores were averaged to create a recognition composite. HVLT-R and BVMT-R delayed recall T-scores were averaged to create a delayed recall composite.

Test-retest reliability estimates of the and HVLT-R recognition ranges from $r = 0.27 – 0.40$ and delayed recall ranges from $r = 0.36 – 0.39$. HVLT-R recognition ($r = 0.48$) and delayed recall ($r = 0.62$) show adequate convergent validity with other tests of verbal memory (i.e., the California Verbal Learning Test; Strauss et al., 2006). The BVMT-R recognition ($r = 0.48 – 0.50$) and delayed recall trial ($r = 0.78 – 0.80$) have been shown to have adequate convergent validity with other tests of visual memory (i.e., WMS-R Visual reproduction and Complex Figure Test; Benedict et al., 1996).

Recognition and delayed recall were initially examined continuously rather than dichotomously splitting participants into impaired versus unimpaired groups. Examining recognition and delayed recall continuously is advantageous because it increases variability and more subtle differences observed in mid-life may not be captured by diagnostic cut-points. However, when examining linear regression analyses from aim 1, the recognition analyses did not meet all assumptions for linear regression (i.e., evidence of heteroscedasticity and residuals were non-normally distributed). Therefore, recognition was dichotomized into an impaired recognition group (i.e., recognition composite Z-score <-1, i.e., < -1 SD below the demographically corrected mean) and an unimpaired recognition group for all analyses.

Processing speed and psychomotor T-scores were used to examine processing speed and psychomotor performance (see Table 2 for specific tests). Raw scores from individual tests were converted to T-scores that adjust for the effect of age, sex, education, race/ethnicity, and practice effects using center-specific (i.e., the HNRP) normative data. The T-scores from all tests in the domain are then averaged to obtain a domain T-score (see Cysique et al., 2011; Heaton et al., 2004; Heaton et al., 2003; Norman et al., 2011 for additional details). The Wide Range

Achievement Test-III (WRAT-III; Wilkinson, 1993), which has been shown to be a measure of premorbid verbal IQ in PWH (Casaletto et al., 2014), was reported to characterize the sample.

2.4 Neuromedical Evaluation

Participants completed a standardized CHARTER neuromedical evaluation at each study timepoint. HIV serostatus was determined by enzyme-linked immunosorbent assay (ELISA) with a confirmatory Western Blot. The following HIV disease characteristics were collected from most participants at each visit: 1) current CD4 count measured via flow cytometry; 2) nadir CD4 measured via a combination of self-report and medical records; 2) CDC HIV staging; 3) HIV RNA in plasma measured by ultra-sensitive PCR (Amplicor, Roche Diagnostic System, Indianapolis IN; lower limit of detection <50 copies/ml); 4) estimated duration of HIV disease collected via self-report; and 5) current ART regimen.

Comorbid medical conditions (e.g., hepatitis C infection (HCV), diabetes, hypertension, hyperlipidemia) were determined by self-report or taking medication for the condition. Comorbid psychiatric and substance use conditions (e.g., major depressive disorder) were determined with the Composite International Diagnostic Interview (World Health Organization, 1997), which is consistent with the DSM-IV. Additional details on the standardized CHARTER neuromedical assessment can be found in Heaton et al. (2010). Additionally, CHARTER participants also have *APOE* genotype data (see Morgan et al. (2013) for additional information). *APOE* genotype was dichotomized into *APOE* ε4+ (i.e., *APOE* genotype ε34 and ε44) and *APOE* ε4- (i.e., *APOE* genotypes ε22, ε23, ε33, ε24).

2.5 Neuroimaging

Image collection. All participants in this study received a structural MRI exam. MRI data were acquired on six General Electric 1.5-Tesla scanners across five sites and annually reviewed for quality. A three-dimensional sagittal T1-weighted-spoiled gradient recalled (SPGR) acquisition was acquired that was used for the FreeSurfer analyses described below. Parameters included: section thickness=1.3mm, FOV 24 cm, matrix size 256 × 256 × 124; TR = 20 ms, TE = 6 ms, flip angle = 30. In addition, coronal 2D T2 and proton density (PD) weighted fast spin echo sequences with a slice thickness of 2.0mm were acquired to allow for true measures of intracranial vault volume that includes sulcal CSF as in previous work (Fennema-Notestine et al., 2013; Fennema-Notestine et al., 2016).

Image processing. FreeSurfer (Dale et al., 1999; Desikan et al., 2006; Fischl, 2012; Fischl et al., 2002) version 7.1.1 was used to obtain cortical thickness and subcortical volume measures for several regions of interest (ROIs), with a similar approach as earlier CHARTER work (Fennema-Notestine et al., 2009; Fennema-Notestine et al., 2011; Lansing et al., 2016). After FreeSurfer processing, all T1 scans were visually inspected; in addition to the one participant excluded from all analyses as described above, one participant's hippocampi were very overestimated, and therefore their hippocampal data were excluded from analyses.

Neocortical thickness regions of interest included medial temporal lobe structures (i.e., entorhinal and parahippocampal), prefrontal (i.e., rostral and caudal midfrontal areas; inferior frontal regions of pars opercularis, pars triangularis, and pars orbitalis), and primary motor (i.e., precentral) cortical areas. Volumetric subcortical regions of interest included the hippocampus (medial temporal lobe structure) as well as the basal ganglia (caudate nucleus and putamen). Specific structures (e.g., entorhinal cortex, hippocampal volume) were analyzed separately. Left

and right volumes or cortical thicknesses for these regions of interest were averaged. In post hoc analyses, if there were significant findings for the average region of interest then the left and right regions were examined separately to examine laterality.

The differences in scanner from site to site was corrected for by regressing scanner from the data, given that differences between scanners have been well-documented in prior CHARTER work (Fennema-Notestine et al., 2007; Jernigan et al., 2011). Differences in head size was accounted for by including estimated total intracranial vault volume (ICV) as a covariate in volumetric data. Mean cortical thickness was included as a covariate in cortical thickness analyses. Additionally, age was included as a covariate to adjust for the normal differences of age on the brain.

2.6 Systemic Inflammation Biomarkers

Five inflammation biomarkers (i.e., Interleukin 6 [IL-6], tumor necrosis factor-α [TNF-α], C-C motif chemokine ligand 2 [CCL2; also known as MCP-1], C-X-C motif chemokine 10 [CXCL10; also known as IP-10], and C-reactive protein [CRP]) were examined in this study. All inflammatory biomarkers have been found to be elevated in the context of HIV and aMCI (Neuhaus et al., 2010; Shen et al., 2019; Wada et al., 2015). Plasma for biomarker assays was collected via routine venipuncture and EDTA vacuum tubes from all participants. All plasma biomarkers were measured using commercially available, multiplex, bead-based immunoassays (Human Luminex Discovery Assay) according to manufacturer protocols; CRP was plated on a separate immunoassay given that it required a different dilution than other plasma biomarkers. Biomarker precision was ensured by assaying specimens in duplicate and repeating measurements with coefficients of variation greater than 20% or outliers that were more than 4

standard deviations from the mean. Additionally, 10% of all assays were repeated to ensure batch consistency. The concentrations of these biomarkers typically have skewed distributions; therefore, the data were log-transformed prior to statistical analysis.

2.7 Data Analytic Approach

Findings were considered significant at $p<0.05$. The false discovery rate method was utilized to correct for multiple-comparisons for the main analyses (Benjamini & Hochberg, 1995). Statistical assumptions were checked prior to all testing. JMP Pro 16 statistical software was used for aim 1, and R version 4.2.1 software was used to examine aims 2 and 3.

Aim 1. Logistic regression was used for dichotomous recognition analyses (i.e., aim 1a and part of aim 1d). Multivariable linear regression was used for continuous outcomes (i.e., delayed recall, processing speed, psychomotor skills T-scores; tested in separate models; lower scores T-scores = worse performance) in aims 1b, 1c, and part of 1d. Primary predictors (i.e., medial temporal lobe, prefrontal thickness, and basal ganglia volume) were tested separately.

Age and imaging covariate (i.e., ICV or mean cortical thickness) were included as covariates in every model. The number of prior neuropsychological evaluations was included as a covariate in recognition models. Additional covariates (e.g., demographics (excluding site given that the effect of scanner was already regressed from the imaging data), comorbidities, HIV disease characteristics, *APOE* status) were selected by evaluating the bivariate relationships between potential covariates and outcomes. If a potential covariate was significantly associated with an outcome at $p<0.10$ it was then entered as a covariate in the model. Given the number of possible additional covariates, these additional covariates (i.e., demographics other than age and site, comorbid conditions, HIV disease characteristics, *APOE* status) were only retained in the

full model if the covariate remained associated with the outcome (via backwards selection) at $p<0.10$. Power analysis was conducted using GPower (Erdfelder et al., 1996). These analyses were powered ($1-\beta = 0.80$) to detect medium effect sizes ($f^2 = .15$), with a two-tailed $\alpha = 0.05$, and up to 5 covariates.

Current CDC guidelines recommend immediately initiating ART and maintaining an undetectable viral load (Centers for Disease Control and Prevention 2021). Despite the fact that only 80% of PWH are engaged in care and 57% of PWH in the United States are virally undetectable (Centers for Disease Control and Prevention, 2019), there is a trend towards examining PWH who are virally suppressed and on ART particularly in studies examining biological processes such as inflammation and neuroimaging (e.g., Montoya et al., 2019; Underwood et al., 2018). Therefore, post hoc analyses examining delayed recall, processing speed, psychomotor skills excluding participants that were not ideally treated for HIV disease (i.e., participants who were not on ART (n=7), had a detectable viral load (n=23)) were excluded. Additionally, given the significant effects of methamphetamine on the brain (Soontornniyomkij et al., 2016), participants who had a current methamphetamine use disorder were also excluded in post hoc analyses (n=2; note: methamphetamine was the only current substance use disorder in the sample at baseline other than alcohol or cannabis; total excluded = 30 given that some participants were excluded for multiple reasons). Dichotomous recognition models were not re-examined given that, with these exclusions, only 7 participants were impaired on the recognition composite.

Aim 2. This aim utilized multi-level modeling to examine recognition and delayed recall across follow-up visits. Outcomes (i.e., recognition and delayed recall) were examined separately. The "lme4 version 1.1-30" R package was used to conduct mixed-effects regressions

(Bates et al., 2014). Mixed-effects logistic regression models were used to examine dichotomous recognition as the outcome. Models examining continuous delayed recall used linear mixed-effects models. Analyses included a random intercept and a random effect for years since baseline (rounded to the tenths place). A cross-level interaction (i.e., time*medial temporal lobe) was used to test if baseline medial temporal lobe structure is associated with longitudinal recognition impairment or decline in delayed recall. Between-persons covariates included: age at baseline, imaging covariate, and covariates identified in aim 1.

Power analysis was conducted using RMASS2 (Hedeker et al., 2016), and observed attrition was accounted for in these estimates. These analyses were found to be powered ($1-\beta = 0.80$) to detect small-to-medium effect sizes ($r^2=0.04$), with a two-tailed $\alpha = 0.05$. Multi-level modeling was selected because it uses all available data and gives heavier weight to participants with more waves of data; thus, this methodology can account for participants that may have missed a follow-up visit and samples that have a differing number of follow-up assessments.

Post hoc delayed recall analyses were conducted that excluded participants who were excluded in post hoc analyses in aim 1 as well as those not consistently on ART and participants with a substance use disorder (other than Alcohol Use Disorder or Cannabis Use Disorder) during follow-up. The total included after these exclusions was n=55.

Aim 3. A single mediator model was used to investigate if medial temporal lobe structures (i.e., hippocampus volume, entorhinal cortex thickness, parahippocampal thickness) had a mediating effect between the peripheral biomarkers of inflammation and recognition and delayed recall. The "lavaan version 0.6-12" R package was used to conduct all mediation analyses (Rosseel, 2012). Inflammation biomarkers were the independent variable (examined

separately), medial temporal lobe structures were the mediator (examined separately), and recognition and delayed recall (examined separately) were the outcomes.

A single mediator model using a robust diagonal weighted least squares approach with bias-corrected bootstrapping to obtain 95% confidence intervals was used for the dichotomous recognition outcome. However, there was poor model fit, and thus logistic regressions were conducted instead to examine if plasma biomarkers of inflammation had a cross-sectional association with recognition. A single mediator model with bias-corrected bootstrapping to obtain 95% confidence intervals were used for the continuous delayed recall outcome. Age, imaging covariate, and other covariates identified in aim 1 were included in analyses. There were not significant associations between plasma biomarkers and delayed recall; however, mediation models were still conducted as there does not need to be a direct effect in order for a mediation effect to be tested or established (Mackinnon & Dwyer, 2016; Shrout & Bolger, 2002).

Delayed recall mediation models were re-examined excluding participants that were excluded from post hoc analyses in aim 1 (i.e., excluding those that were not on ART, participants who had a detectable viral load, and participants with a current methamphetamine use disorder).

3. RESULTS

3.1 Participant Characteristics

Demographic and clinical characteristics are displayed in Table 3. Data presented in Table 3 represents participants' first visit for this analysis, which is when the MRI and blood draw for biomarker analysis were completed. On average, participants were in their early-50s [range = 45 - 68], approximately half were African American/Black, were predominantly male, and had some college education.

With regard to neurocognitive functioning, approximately one-third (32.6%) were classified as neurocognitively impaired via Frascati criteria (Antinori et al., 2007; Heaton 2010). The average T-score for global cognition, recall, and processing speed was around 50, and the average Z-score for recognition was Z=-0.1; however, the average psychomotor skills T-score was lower than average at a T-score of 44. Approximately 20% of the sample was classified as impaired on delayed recall, and 13.2% (n=12) were impaired on recognition. Recognition and delayed recall were correlated at ρ=0.358 (p<0.001). Of the 18 participants that were impaired on delayed recall, 7 were impaired on recognition whereas 11 were not impaired on recognition. Meaning that of the 12 that were impaired on recognition, 7 participants were impaired on delayed recall whereas 5 participants were not impaired on delayed recall.

The majority of participants had HCV, a history of major depressive disorder, and a lifetime history of a substance use disorder (most common were alcohol (56.5%), cocaine (45.6%), cannabis (23.9%), opioid (16.3%), and methamphetamine (11 (12.0%)). Ten participants (11.2%) met criteria for current major depressive disorder and four met criteria for a current substance use disorder (1 alcohol, 1 cannabis, 2 methamphetamine). Approximately one quarter of participants (26.2%) had at least one *APOE* ε4 allele.

Table 3. Participant demographic and neurocognitive characteristics (*N*=92)

	M (SD), median [IQR], n (%)
Demographic Variables	
Age (years), M (SD)	51.4 (5.9)
Male, n (%)	78 (85.7%)
Race/Ethnicity [a]	
African American/Black	46 (50.5%)
Non-Hispanic White	35 (38.4%)
Hispanic/Latino	8 (8.8%)
"Other"	2 (2.2%)
Education (years), M (SD)	13.0 (2.4)
Site	
University of Texas Medical Branch	23 (25.0%)
Mt. Sinai School of Medicine	21 (22.8%)
Johns Hopkins University	18 (19.6%)
University of Washington	16 (17.4%)
University of California San Diego	14 (15.2%)
Baseline Neurocognitive Functioning	
Cognitive Impairment, n (%)	30 (32.6%)
Global T-Score, M (SD)	49.2 (7.1)
Delayed Recall T-Score, M (SD)	50.4 (9.3)
Delayed Recall Impairment, n (%)	18 (19.6%)
HVLT-R Delayed Recall Raw Score, median [IQR]	9 [7-11]
BVMT-R Delayed Recall Raw Score, median [IQR]	9 [7-10.75]
Recognition Z-Score, M (SD)	-0.1 (1.07)
Recognition Impairment, n (%)	12 (13.2%)
HVLT-R Recognition, median [IQR], (range)	11 [10-12], (6-12)
BVMT-R Recognition, median [IQR], (range)	6 [6-6], (4-6)
Processing Speed T-Score, M (SD)	50.5 (9.8)
Psychomotor Skills T-Score [b], M (SD)	44.3 (10.8)
Premorbid Verbal IQ, M (SD)	93 (14.9)

Note. [a] *n*=91; [b] *n*=90; HVLT-R=Hopkins Verbal Learning Test-Revised; BVMT-R=Brief Visuospatial Memory Test-Revised

In terms of HIV disease characteristics, most participants had a history of AIDS, and the median number of years living with HIV was 15.6. Participants' HIV disease was relatively well-controlled, with a median CD4 count of almost 500, and 88.6% were on ART and 73.6% had an undetectable plasma viral load (<50 copies/ml).

Table 4. Participant clinical characteristics (*N*=92)

	M (SD), median [IQR], n (%)
Comorbid Conditions	
Hyperlipidemia [a], n (%)	20 (22.7%)
Hypertension [a], n (%)	36 (40.9%)
Diabetes mellitus [a], n (%)	18 (20.5%)
Hepatitis C [a], n (%)	47 (53.4%)
LT MDD, n (%)	53 (57.6%)
Current MDD, n (%)	10 (10.9%)
LT substance use disorder, n (%)	68 (73.9%)
Current substance use disorder [a], n (%)	4 (4.5%)
APOE Genotype	
APOE ε4+ [a], n (%)	22 (26.2%)
APOE Genotype [a]	
2/2, n (%)	2 (2.3%)
2/3, n (%)	17 (19.3%)
2/4, n (%)	4 (4.5%)
3/3, n (%)	43 (48.9%)
3/4, n (%)	17 (19.3%)
4/4, n (%)	5 (5.7%)
HIV Characteristics	
AIDS, n (%)	68 (73.9%)
Current CD4 [b], median [IQR]	496 [342 – 689]
Nadir CD4, median [IQR]	114 [22 – 214]
Duration of HIV disease (years) [a], median [IQR]	15.6 [9.9 – 19.6]
On ART [a], n (%)	78 (88.6%)
Undetectable viral load [a], n (%)	64 (72.7%)

Note. [a] *n*=88; [b] *n*=87; LT=lifetime; MDD = major depressive disorder; ART = antiretroviral therapy

3.2 Covariate Selection

Age and imaging covariate were included as covariates in all models. Demographic variables (excluding site given that the effect of the scanner was already regressed from the imaging data), comorbid conditions, *APOE* genotype (dichotomized into *APOE* ε4+ and *APOE* ε4-), and HIV disease characteristics in Tables 3 and 4 were considered as covariates. These potential covariates were included in the models if they related to the cognitive outcome at

$p<0.10$ and were retained in the models if they remained related to the outcome at $p<0.10$. See Table 5 for covariates.

Table 5. Covariates by cognitive outcome

Cognitive Outcome	Additional Covariates
Recognition	None
Delayed Recall	*APOE* genotype (dichotomized into ε4+ and ε4-)*, AIDS status*, ART Status, race/ethnicity
Processing Speed	None
Psychomotor	Estimated duration of HIV disease*, viral detectability*, race/ethnicity*, AIDS status

Note. * Indicates the covariates remained associated to the outcome in the full model and were thus included in the models

3.3 Aim 1: To Examine the Neuroanatomical Correlates of Memory Using Structural Neuroimaging Data

Aim 1a. Using logistic regression, medial temporal lobe and basal ganglia structures were not significantly associated with odds of being classified as having a recognition impairment. Within the prefrontal cortex, thinner pars opercularis thickness was associated with greater odds being impaired on recognition (OR=0.336 for every 1 standard deviation increase in pars opercularis thickness, p=0.012); however, this finding was not significant after correcting for multiple comparisons (p=0.060). When examining laterality, thinner left pars opercularis thickness was associated with greater odds of recognition impairment (OR=0.260, p=0.008), whereas the right pars opercularis thickness was not significantly associated with recognition impairment (OR=0.590, p=0.170). No other prefrontal cortex structures were associated with odds of being classified as having a recognition impairment. See Table 6 for model statistics.

Table 6. Logistic regression examining the relationship between the medial temporal lobe, prefrontal cortex, and basal ganglia and likelihood of recognition impairment

	Logit	95% Confidence Interval	Odds Ratio	*p*
Medial Temporal Lobe				
Hippocampus	0.135	[-0.633, 0.891]	1.145	0.725
Entorhinal Cortex	0.156	[-0.512, 0.829]	1.168	0.645
Parahippocampal Gyrus	0.265	[-0.379, 0.943]	1.304	0.425
Prefrontal Cortex				
Caudal Middle Frontal	-0.139	[-1.121, 0.815]	0.870	0.775
Rostral Middle Frontal	-0.480	[-1.377, 0.384]	0.619	0.277
Pars Opercularis	-1.091	[-2.036, -0.235]	0.336	0.012
Pars Triangularis	-0.751	[-1.748, 0.126]	0.472	0.112
Pars Orbitalis	0.329	[-0.398, 1.069]	1.382	0.372
Basal Ganglia				
Caudate Nucleus	0.127	[-0.619, 0.848]	1.136	0.730
Putamen	0.114	[-0.636, 0.833]	1.120	0.759

Note. Logits and odds ratios were calculated for a 1 standard deviation increase in the medial temporal lobe, prefrontal cortex, or basal ganglia volumes. Reference group for recognition is Unimpaired Recognition. All models include age, imaging covariate (ICV or mean cortical thickness), and number of previous neuropsychological assessments.
* $p<0.05$ after correcting for multiple comparisons

Aim 1b. In separate linear regression models including covariates (i.e., age, imaging covariate, *APOE* status, and AIDS status), delayed recall was not significantly associated with medial temporal lobe and basal ganglia structures. Delayed recall was significantly associated with prefrontal thickness. More specifically, thinner rostral middle frontal cortex (β=0.40, p=0.006) and thinner pars opercularis cortex (β=0.46, p=0.001) were associated with worse delayed recall. These associations remained significant even after correcting for multiple comparisons (p=0.005 and p=0.015 respectively). In these two models, AIDS diagnosis (β=0.32, p=0.003; β=0.36, $p<0.001$, respectively) and being *APOE* ε4+ (β=0.19, p=0.061; β=0.28, p=0.007) were associated with worse delayed recall. See Figure 2 for significant relationships between delayed recall and prefrontal structures and Table 7 for model statistics.

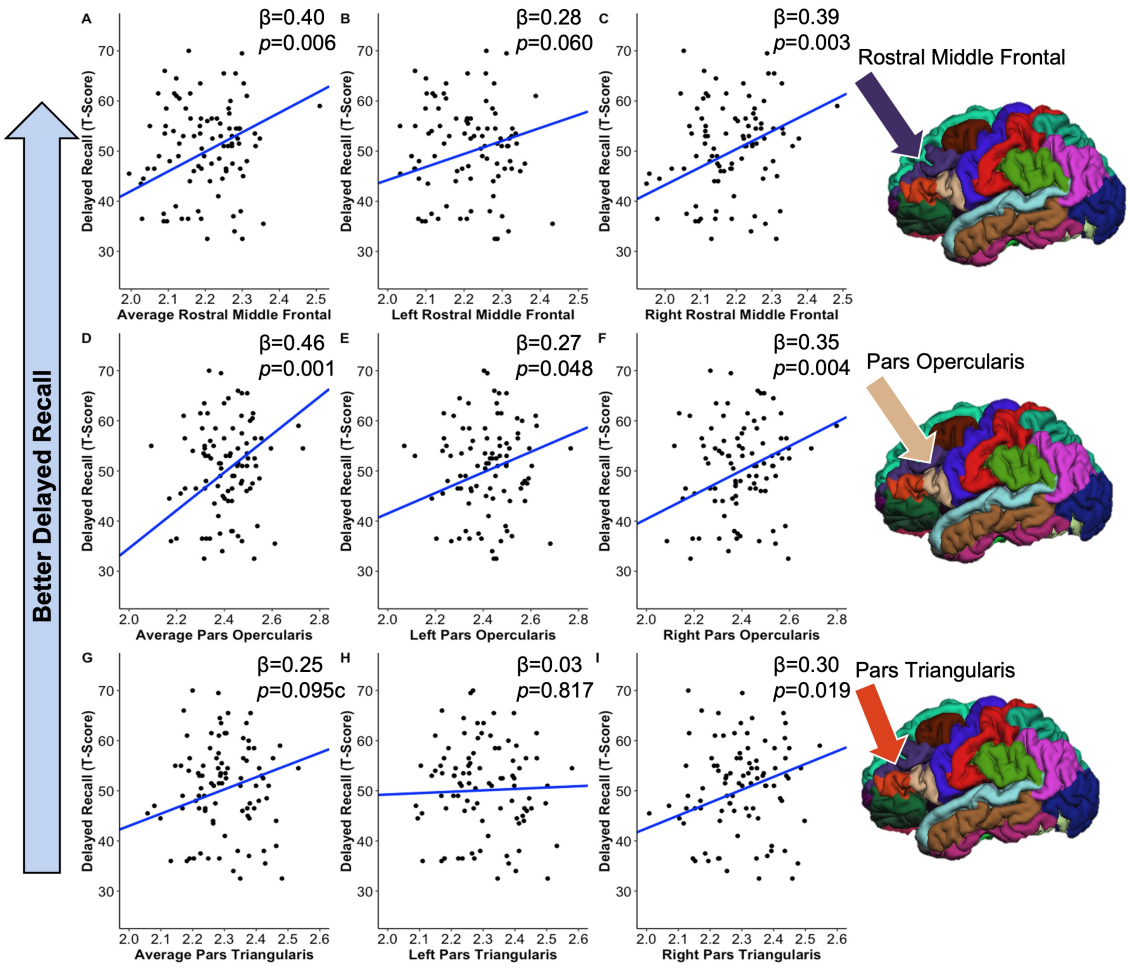

Figure 2. Significant relationships between delayed recall and prefrontal cortex in the entire sample

Note. Regression lines adjust for age (centered), AIDS Status (reference: non-AIDS), APOE group (reference: APOE ε4- group) and mean cortical thickness (centered).

When examining laterality, the right rostral middle frontal cortex (β=0.39, *p*=0.003) was somewhat more associated with delayed recall in comparison to the left (β=0.28, *p*=0.060). The right pars opercularis (β=0.35 *p*=0.004) was somewhat more associated with delayed recall than the left (β=0.27, *p*=0.048). Other prefrontal regions were not significantly associated with delayed recall, except for the right pars triangularis (β=0.30, *p*=0.019), which was significantly associated with delayed recall whereas the average pars triangularis (β=0.25, *p*=0.095) and the left pars triangularis (β=0.03, *p*=0.817) were not.

Table 7. Multivariable linear regressions examining the relationship between the medial temporal lobe, prefrontal cortex, and basal ganglia and delayed recall

	Beta	95% Confidence Interval	Std. Beta	*p*	Model R^2
Medial Temporal Lobe					
Hippocampus	0.143e-2	[-0.552e-2, 0.838e-2]	0.053	0.683	0.109
Entorhinal Cortex	-5.428	[-14.211, 3.355]	-0.136	0.222	0.145
Parahippocampal Gyrus	0.557	[-9.647, 10.762]	0.012	0.914	0.129
Prefrontal Cortex					
Caudal Middle Frontal	4.759	[-19.686, 29.203]	0.063	0.700	0.131
Rostral Middle Frontal	38.986	[11.538, 66.433]	0.397	0.006*	0.206
Pars Opercularis	37.813	[14.999, 60.627]	0.457	0.001*	0.231
Pars Triangularis	24.321	[-4.347, 52.989]	0.249	0.095	0.158
Pars Orbitalis	-1.064	[-19.728, 17.600]	-0.013	0.910	0.129
Basal Ganglia					
Caudate Nucleus	-0.714e-2	[-1.739e-2, 0.312e-2]	-0.161	0.170	0.143
Putamen	-0.331e-2	[-0.808e-2, 0.147e-2]	-0.160	0.172	0.143

Note. All models include age, imaging covariate (ICV or mean cortical thickness), AIDS Status, and *APOE* status.
* $p<0.05$ after correcting for multiple comparisons

These relationships were re-examined excluding participants who were on not ART, those who had a detectable viral load, and those with a current methamphetamine use disorder. Thinner entorhinal cortex thickness was significantly related to better delayed recall functioning (β=-0.39, p=0.006); this relationship was somewhat stronger on the left (left entorhinal cortex β=-0.40, p=0.005; right entorhinal cortex β=-0.265, p=0.051; see Figure 3). Other medial temporal lobe structures remained non-significantly related to delayed recall (ps>0.408). Basal ganglia volumes were not significantly related to delayed recall (ps>0.417). Regarding, prefrontal structures, the results did not significantly change from previous analyses as thinner rostral middle frontal (β=0.58, p=0.004) and thinner pars opercularis (β=0.47, p=0.016) remained significantly associated with worse delayed recall, with associations being somewhat stronger in

the right hemisphere. Other prefrontal structures were not associated with delayed recall (*p*s>0.156).

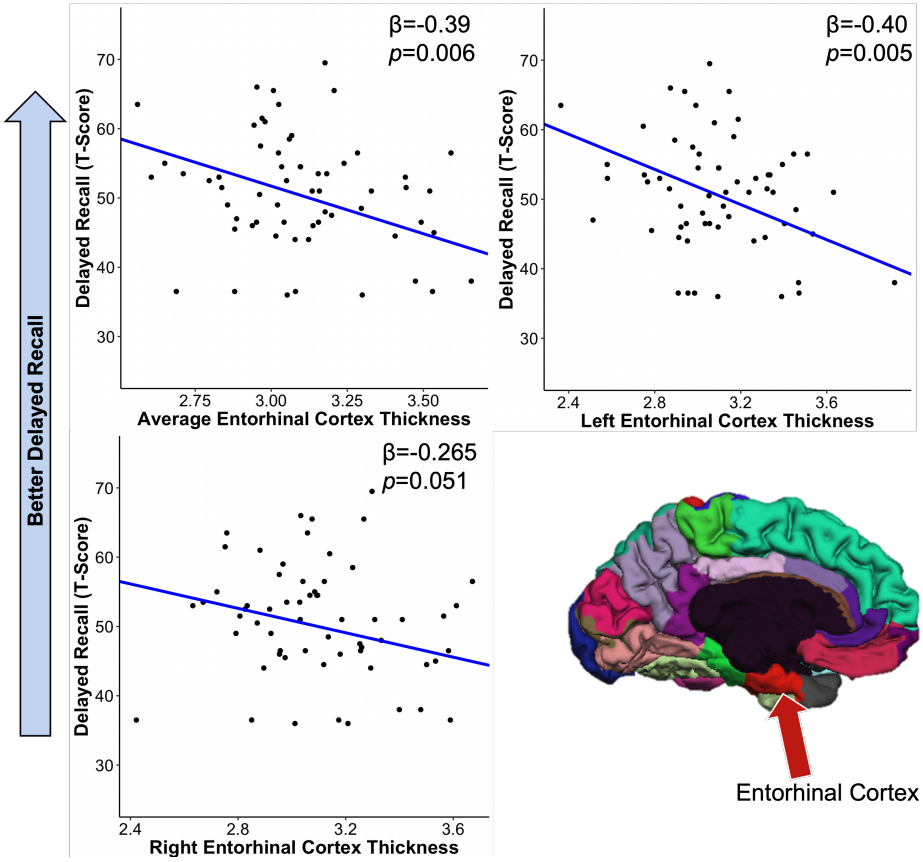

Figure 3. Relationship between delayed recall and entorhinal cortex thickness in the post hoc sample excluding participants not on ART, those with a detectable viral load, or with methamphetamine use disorder (*n*=62)
Note. Regression lines adjust for age (centered), AIDS Status (reference: non-AIDS), *APOE* status (reference: *APOE* ε4- group), and mean cortical thickness (centered).

Aim 1c. Processing speed and psychomotor functioning were not associated with the medial temporal lobe, the prefrontal cortex, or the basal ganglia in multivariable linear regressions. See Table 8 for statistics. Models were re-run excluding those who were not on ART, had a detectable viral load, and those with a current methamphetamine use disorder, and results for processing speed remained non-significant (processing speed: *p*s>0.131). When models examining psychomotor functioning were re-analyzed excluding those participants,

thinner pars orbitalis was significantly associated with worse psychomotor functioning (β=0.28, *p*=0.044). Psychomotor functioning was not significantly associated with the medial temporal lobe, the basal ganglia, or other prefrontal cortex structures (*p*s>0.090).

Table 8. Multivariable linear regressions examining the relationship between the medial temporal lobe, prefrontal cortex, and basal ganglia, processing speed and psychomotor functioning

	Beta	95% Confidence Interval	Std. Beta	*p*	Model R^2
Medial Temporal Lobe					
Hippocampus					
Processing Speed	0.284e-2	[-0.447e-2, 1.016e-2]	0.098	0.442	0.066
Psychomotor	0.315e-2	[-0.568e-2, 1.197e-2]	0.096	0.353	0.157
Entorhinal Cortex					
Processing Speed	0.421	[-8.940, 9.782]	0.010	0.929	0.030
Psychomotor	-4.442	[-14.764, 5.879]	-0.095	0.394	0.244
Parahippocampal Gyrus					
Processing Speed	-2.233	[-12.753, 8.285]	-0.046	0.674	0.031
Psychomotor	-3.053	[-14.380, 8.275]	-0.058	0.593	0.235
Prefrontal Cortex					
Caudal Middle Frontal					
Processing Speed	-9.600	[-35.322, 16.121]	-0.121	0.460	0.036
Psychomotor	22.179	[-7.616, 51.975]	0.248	0.142	0.247
Rostral Middle Frontal					
Processing Speed	6.699	[-23.863, 37.262]	0.064	0.664	0.032
Psychomotor	23.543	[-11.292, 58.377]	0.200	0.182	0.242
Pars Opercularis					
Processing Speed	15.662	[-9.798, 41.122]	0.179	0.225	0.046
Psychomotor	9.516	[-18.154, 37.185]	0.099	0.495	0.234
Pars Triangularis					
Processing Speed	4.082	[-24.817, 32.982]	0.041	0.780	0.030
Psychomotor	6.813	[-24.532, 38.158]	0.062	0.666	0.232
Pars Orbitalis					
Processing Speed	-13.712	[-33.123, 5.700]	-0.165	0.164	0.051
Psychomotor	8.838	[-12.495, 30.170]	0.096	0.412	0.237
Basal Ganglia					
Caudate Nucleus					
Processing Speed	0.719e-2	[-0.316e-2, 1.753e-2]	0.162	0.171	0.075
Psychomotor	0.0361e-2	[-1.153e-2, 1.226e-2]	0.007	0.948	0.171
Putamen					
Processing Speed	0.334e-2	[-0.148e-2, 0.815e-2]	0.161	0.172	0.074
Psychomotor	0.015e-2	[-0.539e-2, 0.568e-2]	0.006	0.956	0.170

Note. Models include age and imaging covariate (ICV or mean cortical thickness). Psychomotor models also include estimated duration of HIV disease, viral detectability, and race/ethnicity.

Aim 1d. Neither recognition nor delayed recall were associated with the primary motor cortex (i.e., precentral gyrus thickness; see Table 9). When examining delayed recall in participants who were on ART, without a detectable viral load, and without a current methamphetamine use disorder, the results remained non-significant (*p*s>0.609).

Table 9. Logistic regression and multivariable linear regression examining the relationship between the precentral gyrus, likelihood of recognition impairment, and delayed recall

	Logit or Beta	95% Confidence Interval	Odds Ratio or Std. Beta	*p*
Precentral Gyrus				
Recognition	Logit=-0.196	[-1.078, 0.492]	OR=0.822	0.622
Delayed Recall	B= -3.195	[-19.206, 12.815]	β= -0.046	0.692

Note: Logit and odds ratio for recognition were calculated for a 1 standard deviation increase in precentral gyrus thickness. Reference group for recognition is unimpaired recognition. All models include age and mean cortical thickness. Recognition models include number of previous neuropsychological assessments. Delayed recall models include AIDS Status and *APOE* group.

3.4 Aim 2: To Examine if Baseline Structural Neuroimaging Predicts Amnestic Decline

On average, participants were seen for 5.7 (range: 0 – 11) follow-up neuropsychological and neuromedical visits. Participants were followed for an average of 6.5 years (range: 0 – 11.9 years). At the last follow-up visit, participants were on average 57.6 years old (SD = 6.9).

Regarding HIV disease characteristics over time, 36 of 91 (39.6%) with at least 1 follow-up visit had a consistently undetectable viral load (<50 copies/ml; not including 67 counts of missing data). Of the 55 participants with at least one timepoint in which they were virally detectable, these participants were virally undetectable in plasma at 50.6% of visits (median = 448 copies/mL, IQR=133 – 13006). Sixty-nine of 91 participants (75.8%) were on ART for all visits (excluding 16 counts of missing data.) For participants with variable ART use, they were, on average, on ART for 63.7% of visits (range: 0% - 90%). No participants converted to AIDS.

Regarding substance use, 75 of 91 participants never met criteria for a substance or alcohol use disorder during the study (excluding 9 counts of missing data). Of participants that did have a substance use disorder at some point, they had a substance or alcohol use disorder at 28% of visits (range 11% - 83%). Six met criteria for alcohol use disorder, three for cannabis use disorder, three for methamphetamine use disorder, three cocaine use disorder, one for sedative use disorder, and one for other substance use disorder.

Recognition. Of the 12 participants who were impaired in recognition at baseline, only two were impaired across all follow-up visits. Two of the 12 participants were not impaired at any subsequent visit, and the other eight were impaired between 25% and 86% of follow-up visits. Of the 79 participants who unimpaired in recognition at baseline, 44 were unimpaired for all visits. Of the participants who had at least one follow-up visit in which they were impaired in recognition, they were impaired between 10% and 100% of visits (median = 25%). Most participants who were impaired in recognition reverted to unimpaired recognition at their subsequent visit, and only four participants showed consistent recognition impairment. However, these participants had a limited follow-up after the initial recognition impairment (i.e., 1-2 visits).

In building the model to examine if baseline medial temporal lobe structures predict a decline in recognition, the simplest random-slope and random-intercept model (i.e., with no additional covariates) did not converge and some dimensions of the variance-covariance matrix were estimated at exactly 0. This indicates poor model fit with too many specified parameters and the cross-level interaction cannot be examined using this method. Nevertheless, recognition composite values across time are depicted in Figure 4.

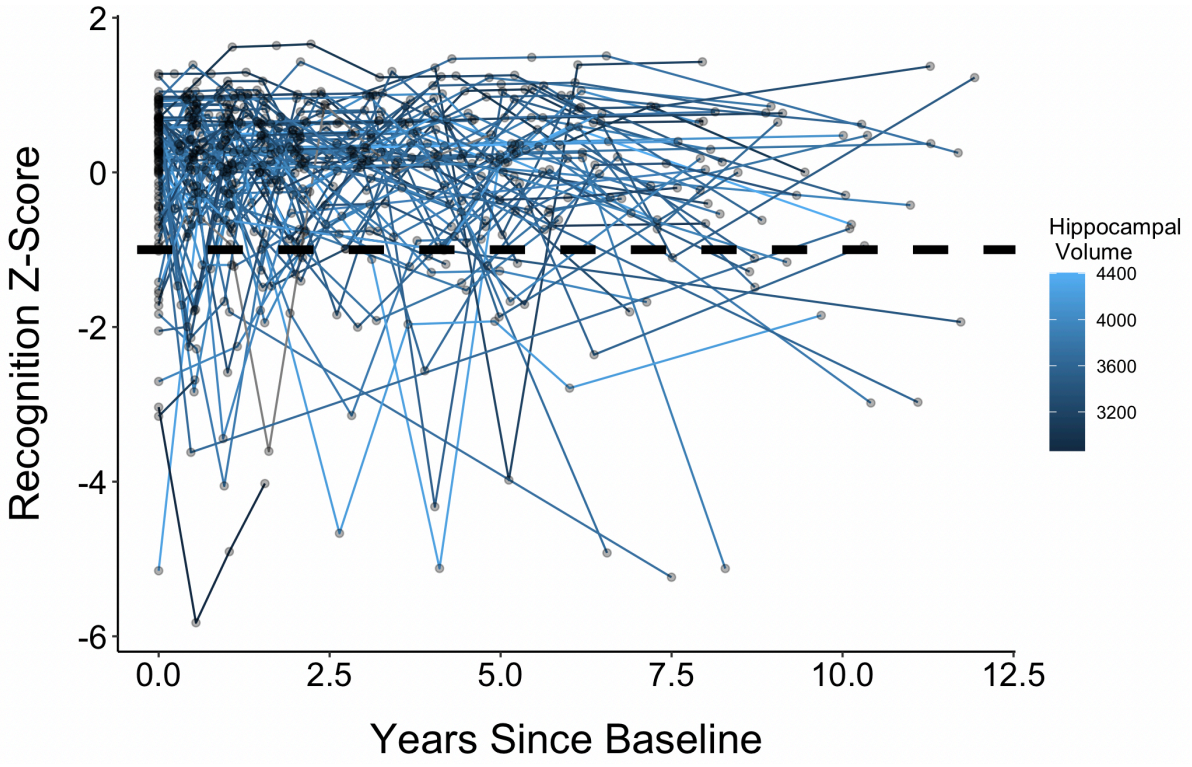

Figure 4. Recognition compositve Z-scores graphed across years since baseline
Note. Dashed line depicts the -1 standard deviation cut-off. Participant visits below this line were impared on recogniton.

Delayed Recall. The intraclass correlation (ICC) for delayed recall derived from the intercept-only model equaled 0.68 (i.e., 58.34/(58.34 + 28.08)), indicating that 68% of the variability in the delayed recall scores could be attributed to the between-person differences in average delayed recall performance.

In the random slopes and random intercept model with no additional covariates, the average slope was -0.041, indicating that, on average, the delayed recall T-score decreased by 0.041 every year. The standard deviation of the slope was 0.678.

In the random slopes and random intercept model including all covariates (i.e., imaging covariate, age, *APOE* status, and AIDS status), none of the years since baseline by MTL cross-

level interactions were significant (*p*s>0.412). See Table 10 for full model statistics. Delayed recall scores across time and slope are depicted in Figure 5.

Table 10. Linear mixed-effects results examining whether baseline medial temporal lobe structures are associated with change in delayed recall

	Estimate	95% Confidence Interval	*p*
Hippocampus			
Within-Person Level			
Years Since Baseline	1.162	[-1.677, 4.040]	0.430
Between-Person Level			
Baseline Age (mean centered)	-0.048	[-0.354, 0.258]	0.766
Hippocampal Volume (standardized)	12.861	[-11.838, 37.824]	0.324
ICV (standardized)	-1.413	[-3.727, 0.891]	0.243
APOE (ref: 4-)	-2.406	[-7.196, 2.382]	0.341
AIDS Status (ref: AIDS)	5.883	[1.549, 0.102]	0.012
Cross-Level Interaction			
Hippocampal Volume*Years Since Baseline	-1.178	[-4.051, 1.664]	0.424
Entorhinal Cortex			
Within-Person Level			
Years Since Baseline	0.259	[-3.054, 3.622]	0.880
Between-Person Level			
Baseline Age (mean centered)	-0.075	[-0.369, 0.220]	0.627
Entorhinal Cortex (standardized)	-1.370	[-3.252, 0.514]	0.169
Mean Cortical Thickness (standardized)	-1.061	[-2.940, 0.822]	0.285
APOE (ref: 4-)	-4.500	[-9.0580, 0.056]	0.063
AIDS Status (ref: non-AIDS)	6.217	[2.049, 10.398]	0.006
Cross-Level Interaction			
Entorhinal Cortex*Years Since Baseline	-0.019	[-0.264, 0.224]	0.880
Parahippocampal Cortex			
Within-Person Level			
Years Since Baseline	-1.313	[-4.419, 1.829]	0.414
Between-Person Level			
Baseline Age (mean centered)	-0.072	[-0.372, 0.228]	0.647
Parahippocampal Cortex (standardized)	-0.562	[-2.551, 1.424]	0.592
Mean Cortical Thickness (standardized)	-1.365	[-3.350, 0 0.622]	0.195
APOE (ref: 4-)	-3.744	[-8.277, 0.788]	0.119
AIDS Status (ref: non-AIDS)	6.174	[1.935, 10.425]	0.007
Cross-Level Interaction			
Parahippocampal Cortex*Years Since Baseline	0.107	[-0.148, 0.359]	0.412

Note: ICV = intracranial volume

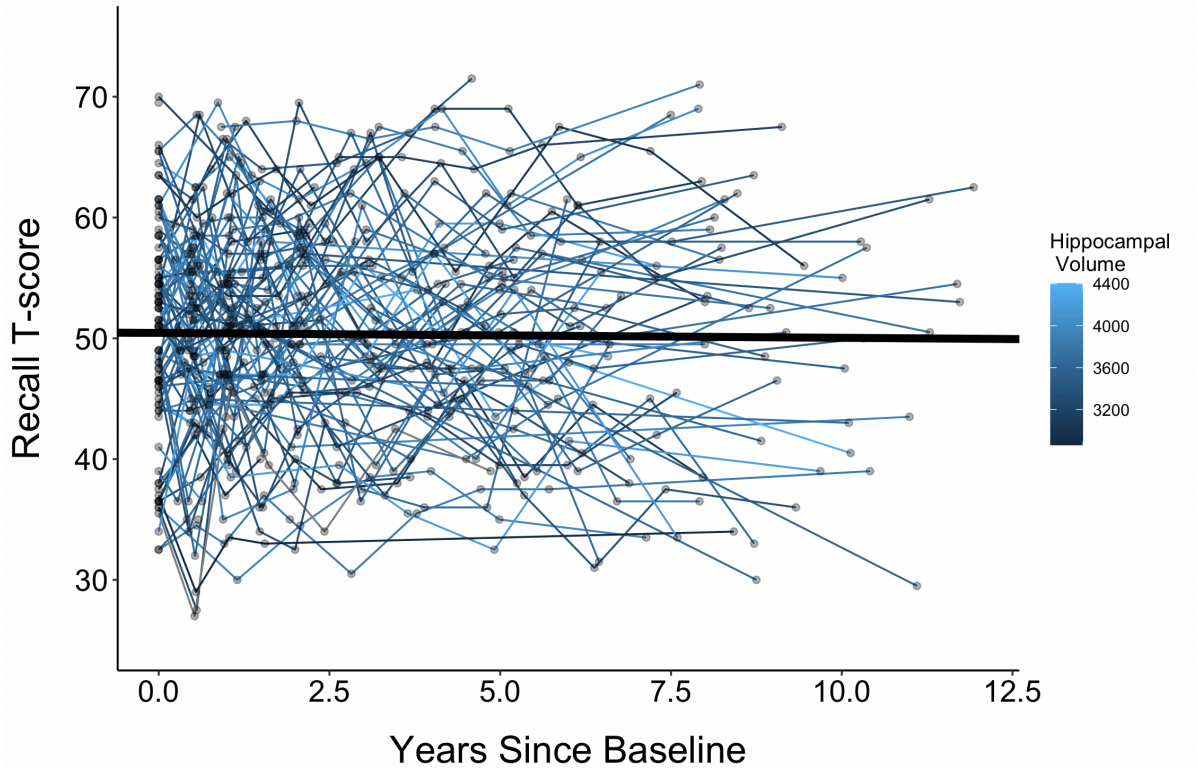

Figure 5. Delayed recall T-Scores graphed across years since baseline
Note. The black line depicts the average change in delayed recall over time (i.e., slope).

Post hoc sensitivity analyses excluding participants who were excluded in post hoc analyses in aim 1 (i.e., those not on ART, with detectable viral load, and those with current methamphetamine use disorder) as well as those not consistently on ART and participants with a substance use disorder other than Alcohol Use Disorder and Cannabis Use Disorder were conducted (*n*=55). The ICC for the delayed recall derived from the intercept-only model equaled 0.67 (i.e., 54.19/(54.19+27.19)), indicating that 67% of the variability in the delayed recall scores could be attributed to the between-person differences in average delayed recall performance. In the random slopes and random intercept model with no additional covariates, the average slope was -0.154, indicating that, on average, the delayed recall T-score decreased by 0.154 every year,

and the standard deviation of the slope was 0.802. None of the cross-level interactions were significant, indicating that in this smaller group of participants that baseline hippocampal volume (B= -0.096, *p*=0.594), entorhinal cortex thickness (B=0.001, *p*=0.995), and parahippocampal cortex thickness (B=0.099, *p*=0.555) did not moderate delayed recall performance over time.

3.5 Aim 3: To Examine if the Medial Temporal Lobe Mediates a Relationship Between Peripheral Inflammation and Memory

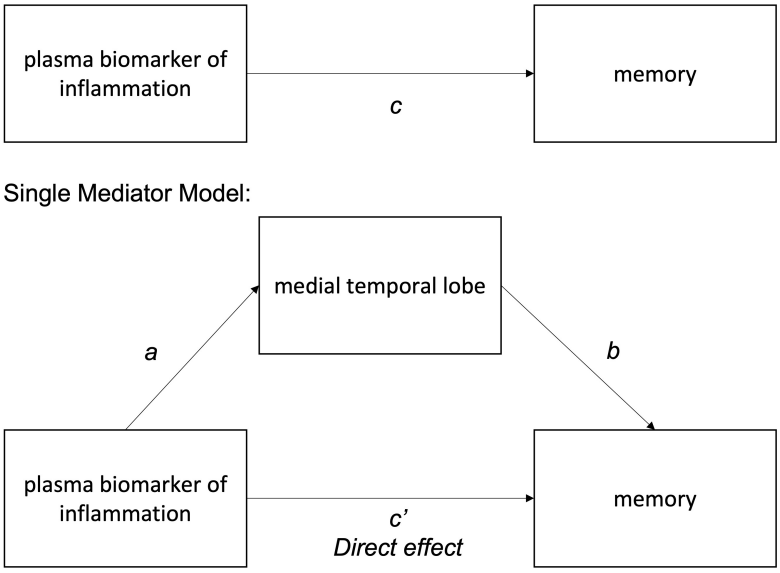

Figure 6. Single mediator model to examine if medial temporal lobe structures mediate the relationship between plasma biomarkers of inflammation and memory (i.e., recognition and delayed recall)

For this aim, a single-mediator model examined if medial temporal lobe structures (i.e., hippocampus volume, entorhinal cortex thickness, parahippocampal thickness) had a mediating effect between inflammation biomarkers (i.e., IL-6, TNF-α, CCL2, CRP, and CXCL10) and memory (i.e., dichotomous recognition or continuous delayed recall) as depicted in Figure 6. Average levels of the plasma biomarkers of inflammation are displayed in Table 11.

Table 11. Mean and standard deviation of the plasma biomarkers of inflammation

Biomarker	Mean (SD)
IL-6	0.650 (0.201)
TNF-α	1.027 (0.305)
CCL2	2.343 (0.165)
CRP	6.143 (0.555)
CXCL10	1.734 (0.347)

Note. Biomarkers of inflammation are log-transformed

Recognition. When examining recognition using a single mediator model using robust diagonal weighted least squares, all mediation models produced an error indicating that at least one correlation in the correlation matrix between the medial temporal lobe and recognition was nearly 1.0. Overall, this indicates poor model fit. Therefore, mediation statistics are not reported.

Therefore, the total effect between the five biomarkers of inflammation and dichotomized recognition was examined using logistic regression. When accounting for age and number of previous neuropsychological assessments, greater levels of plasma CRP were associated with lower odds of having impaired recognition at baseline (OR=0.419 for a 1-unit increase in log-transformed CRP, p=0.010; depicted in Figure 7). No other biomarkers of inflammation were significantly associated with recognition impairment. See Table 12 for model statistics.

Table 12. Logistic regression examining the relationship between the peripheral inflammation and likelihood of recognition impairment

	Logit	**95% Confidence Interval**	**Odds Ratio**	***p***
IL-6	-0.266	[-0.906, 0.360]	0.767	0.404
TNF-α	-0.176	[-0.723, 0.453]	0.839	0.547
CCL2	0.535	[-0.095, 1.235]	1.707	0.112
CRP	-0.871	[-1.599, -0.244]	0.419	0.010*
CXCL10	-0.309	[-1.075, 0.328]	0.734	0.384

Note. Biomarkers of inflammation are log-transformed. Models include age and number of previous neuropsychological assessments. * p<0.05 after correcting for multiple comparisons

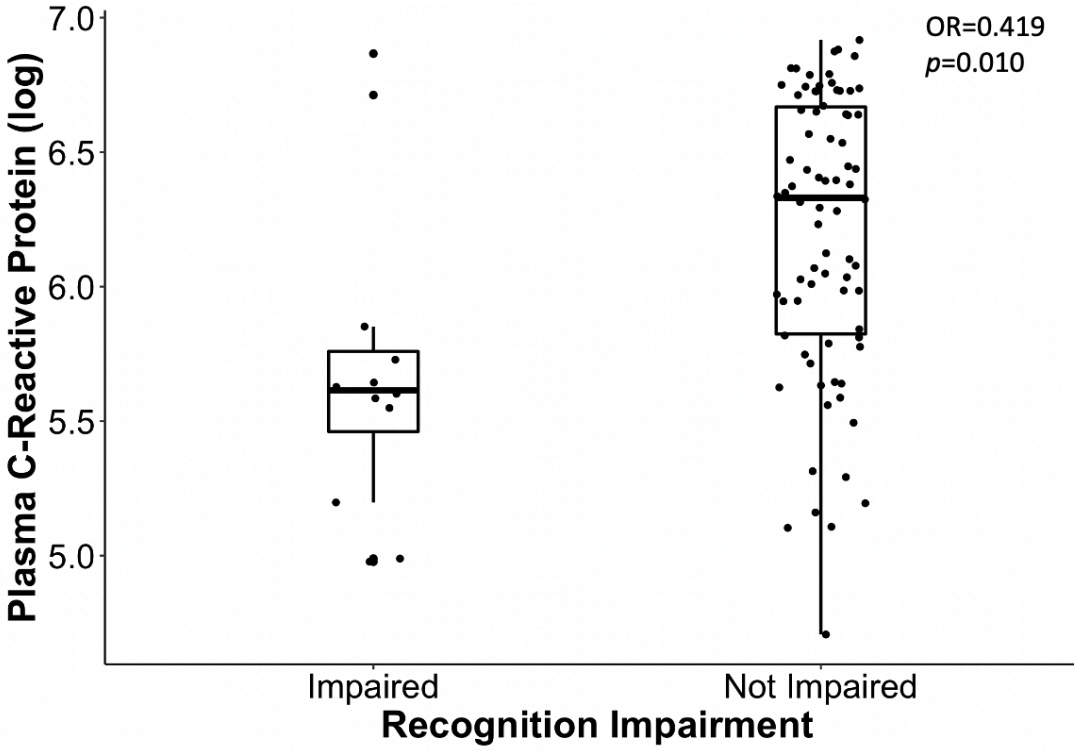

Figure 7. Box plot showing distribution of log-adjusted plasma C-Reactive Protein (CRP) by recognition impairment group.

Delayed recall. A single-mediator model that accounted for relevant covariates (i.e., age, imaging covariate, *APOE* group, and AIDS status) was used. No significant direct effects from any plasma biomarkers of inflammation to delayed recall were found (*p*s>0.078). None of the plasma biomarkers of inflammation were significantly associated with any of the medial temporal lobe structures (i.e., path *a*; *p*s>0.116), and none of the medial temporal lobe structures were significantly associated with delayed recall (i.e., path *b*; *p*s>0.193). When examining the indirect effect, all bias-corrected 95% CI contained 0; therefore, no meditated effect was established. See Table 13 for direct and indirect effects.

Post hoc analyses excluding participants who were not on ART, with detectable viral load, and those with methamphetamine were examined. Accounting for covariates, no significant

direct effects from any plasma biomarkers of inflammation to delayed recall were found (*p*s>0.205). Greater plasma CRP was associated with a thinner parahippocampal gyrus (B= -0.128, *p*=0.004), but no other plasma biomarkers of inflammation were significantly associated with any of the medial temporal lobe structures (i.e., path *a*; *p*s>0.203). As demonstrated in aim 1, a thinner entorhinal cortex was associated with better delayed recall performance (*p*s<0.010), but no other medial temporal lobe structures were significantly associated with delayed recall (i.e., path *b*; *p*s>0.203). When examining the indirect effects, all bias-corrected 95% CI contained 0; therefore, no meditated effect was established.

Table 13. Direct and indirect effects for a single-mediator model examining if medial temporal lobe structures mediate the relationship between plasma biomarkers of inflammation and delayed recall

	Direct effect (c')	**c' *p*-value**	**Indirect effect (ab)**	**95% Confidence Interval**
Hippocampus				
IL-6	0.535	0.912	-0.103	[-2.142, 0.872]
TNF-α	0.289	0.921	0.156	[-0.457, 2.274]
CCL2	-2.462	0.695	-0.566	[-6.300, 1.391]
CRP	3.439	0.078	-0.078	[-1.137, 0.278]
CXCL10	1.023	0.659	-0.037	[-1.332, 0.845]
Entorhinal Cortex				
IL-6	0.911	0.846	-0.490	[-3.821, 0.749]
TNF-α	0.783	0.796	-0.424	[-2.468, 0.241]
CCL2	-4.110	0.535	0.715	[-0.621, 4.409]
CRP	2.483	0.130	-0.004	[-1.068, 0.636]
CXCL10	0.770	0.730	0.146	[-0.479, 1.577]
Parahippocampal Gyrus				
IL-6	0.349	0.940	0.073	[-1.230, 2.797]
TNF-α	0.335	0.909	0.024	[-0.763, 1.187]
CCL2	-3.649	0.580	0.254	[-1.857, 3.138]
CRP	2.585	0.145	-0.106	[-1.191, 0.379]
CXCL10	0.770	0.730	0.146	[-0.479, 1.577]

Note. Biomarkers of inflammation are log-transformed. Models include age, MRI covariate (ICV or mean cortical thickness), *APOE* group, and AIDS Status.

4. DISCUSSION

This study closely examined episodic memory (i.e., recognition and delayed recall) and the biological correlates of episodic memory. This is one of the first studies to examine the relationship between episodic memory, particularly recognition, and brain integrity both cross-sectionally and longitudinally in middle-aged PWH without significant confounding comorbid conditions. This study had the potential to help validate recognition as a clinical marker that could aid in distinguishing aMCI and an AD trajectory from HAND, which could have led to diagnostic improvements in disentangling HAND and aMCI. While this study did not support that recognition is associated with more AD-related markers (i.e., the medial temporal lobe), it did demonstrate that episodic memory in middle-aged PWH is possibly related to frontally mediated etiologies, such as HIV, and that there was little decline in episodic memory in this group. Moreover, this is one of the first to examine the role of peripheral inflammation and its association with brain integrity and episodic memory in middle-aged and older PWH, although there were few associations with peripheral inflammation. While many of the findings of this study were not in line with the hypotheses, these findings are still clinically important and help to address gaps in our understanding of the biological associations of episodic memory in middle-aged PWH.

4.1 Cross-Sectional Neuroanatomical Correlates of Memory, Processing Speed, and Psychomotor Functioning

4.1.1 The neuroanatomical correlates of episodic memory. Broadly, the first aim of this study was to examine how recognition and delayed recall were associated with the medial temporal lobe, which is more implicated in preclinical AD, and the basal ganglia and prefrontal

cortex, which are more associated with HAND. Aim 1a examined the relationship between recognition and these three regions of interest. It was hypothesized that recognition memory would be more strongly related to medial temporal lobe structures given that recognition memory deficits are more associated with AD. Because recognition scores were skewed, as is common given that most people attain a near-perfect score with low variability in scores, this variable was dichotomized as examining it continuously violated multivariable linear regression assumptions. In this sample of 92 participants, only 12 (13.2%) of participants were impaired on recognition. As discussed later, this sample of PWH may not be generalizable and thus the group that was impaired on recognition is both small and may also not be generalizable to other groups; additionally, recognition impairment at baseline may not be reliable given the instability of the recognition impairment across visits.

Contrary to the hypothesis, medial temporal lobe structures were not significantly associated with odds of being impaired on recognition. Given the limited number of participants that were impaired on recognition, there may not have been enough power to detect an effect; however, the odds ratios were fairly close to 1 indicating the association was neither statistically nor clinically significant. Also contrary to the aim 1a hypothesis, a thinner pars opercularis, part of the prefrontal cortex, was significantly associated with greater odds of being impaired on recognition. No other prefrontal regions or basal ganglia regions were significantly associated with odds of being impaired on recognition.

Aim 1b examined the relationship between continuous delayed recall and the three regions of interest. Delayed recall was hypothesized to be more equally associated with all three regions, given that delayed recall deficits are observed in both aMCI/AD and HAND. Somewhat consistent with the hypothesis, thicker rostral middle frontal gyrus and pars opercularis were

associated with better delayed recall. Examining laterality, these findings were somewhat more driven by the right. Additionally, thicker right pars triangularis was significantly associated with better delayed recall whereas the left pars triangularis was not. Contrary to the hypothesis, delayed recall was not significantly associated with the medial temporal lobe nor the basal ganglia. In post hoc analyses that excluded participants not on ART, or those with a detectable viral load or methamphetamine use disorder – a group of participants who are closer to those who are ideally treated in medical care – these associations held and thicker rostral middle frontal gyrus and pars opercularis were associated with better delayed recall and relationships were somewhat stronger within this subset of participants. It is important to note that given that delayed recall was examined continuously, this does not imply that these prefrontal regions are associated with delayed recall impairment, as that was not examined. Moreover, mean cortical thickness was included in the models as a covariate, so this means that this association is observed while accounting for average cortical thickness.

Taken together, the finding that episodic memory was associated with some prefrontal structures may suggest that, at least in middle age, episodic memory performance is more likely related to frontally mediated etiologies, such as HIV, rather than early AD pathology. The inferior frontal gyrus, which includes the pars opercularis, pars triangularis, and pars orbitalis, as well as the middle frontal gyrus are not part of the medial limbic circuit (i.e., Papez circuit) implicated in memory formation, but they still contribute to memory deficits. The prefrontal cortex is of course associated with memory retrieval (Aggleton et al., 2022; Preston & Eichenbaum, 2013). Additionally, more recent models of memory formation stress the importance of the prefrontal cortex in memory formation given that there is some research to suggest that the prefrontal cortex aids in enabling long-term memory formation through

connections with the anterior thalamic nuclei (Aggleton et al., 2022). Additionally, these more updated models of memory formation could account for why recognition was associated with prefrontal structures as well, although there could be several other explanations for this observed association. For example, recognition may also be associated with prefrontal structures due to poor initial encoding, which was not explicitly examined in these analyses. Nevertheless, functional MRI studies have shown alterations in prefrontal and hippocampal regions during memory tasks in PWH compared to controls further highlighting that prefrontal regions are implicated in memory in PWH (Hakkers et al., 2017).

As highlighted in the introduction, HIV studies have found structural changes throughout the brain, including frontal regions, as compared to persons without HIV (Ances & Hammoud, 2014; Holt et al., 2012). Additionally, studies have demonstrated accelerated age-related atrophy or greater than expected "brain age" in middle-aged and older PWH compared to HIV-negative participants (Clifford et al., 2017; Cole et al., 2017; Holt et al., 2012; Milanini et al., 2019; Pfefferbaum et al., 2014). For example, Milanini et al., 2019 found that, in a group of 19 participants with HAND who were on average 64 years old, HAND individuals showed faster atrophy in the cerebellum and frontal gray matter compared to HIV-negative controls. Additionally, Pfefferbaum et al., 2014 found accelerated changes in the frontal lobe, temporal pole, parietal lobe, and the thalamus in PWH (mean age = 45) compared to HIV-negative controls. Of these studies examining longitudinal brain changes, all found some involvement of the frontal lobe, but most studies did not examine the specific regions within frontal lobe that were driving these associations. Additionally, results from these studies were mixed as to if brain changes were associated with changes in cognition. Given that the current study only examines structural MRI at one timepoint, we cannot assume that there has been atrophy of the prefrontal

cortex; however, given the literature demonstrates atrophic changes in PWH in the frontal lobe and accelerated aging in the frontal lobe, is possible that changes in the prefrontal cortex have occurred in this cohort and are contributing to the observed associations with memory.

One debate in the HIV literature is the extent to which HIV disease is associated with accelerated aging as opposed to other comorbid conditions or other lifestyle factors associated with HIV. However, it is difficult to differentiate the effect of HIV itself versus the downstream effects of HIV (e.g., increased risk of cerebro/cardiovascular disease) or lifestyle factors associated with risk of contracting HIV (e.g., intravenous drug use). For example, many studies have documented higher risk of vascular risk factors including hyperlipidemia, type II diabetes, hypertension, and abdominal obesity in PWH likely due to the cardiometabolic side effects of ART, chronic immune activation, comorbid conditions that are more common in PWH (e.g., tobacco use, HCV), and increased risk of chronic stressors (Cysique & Brew, 2019; McIntosh et al., 2021). Cysique & Brew (2019) propose that vascular cognitive impairment is implicated in the pathogenesis of neurocognitive impairment in PWH, particularly older PWH, given that cardiovascular and cerebrovascular conditions can cause alterations in the blood-brain barrier, altered vascular reactivity, and brain changes, particularly in white matter. A recent meta-analysis by McIntosh et al., (2021) found that cardiovascular disease, particularly type II diabetes, hyperlipidemia, and current smoking, are associated with an increased risk of cognitive impairment in PWH. CVD has been associated with brain changes in PWH, but the majority find an association with abnormal white matter (Calon et al., 2020; Holt et al., 2012; Samboju et al., 2021), which was not examined in the current study. Several vascular risk factors were examined as covariates and were not found to be significantly associated with cognitive outcomes; although it is important to note that this group is limited in that participants with more significant

vascular comorbidities such as stroke or myocardial infarction were excluded for these analyses. Nevertheless, further exploration of vascular risk factors and how they are associated with cognition and brain aging in this cohort and PWH more broadly is of course warranted to further understand the effects of HIV versus the effects of comorbid conditions associated with HIV.

Comparing the results of the current study to the middle-aging literature is difficult. First, while brain changes due to AD pathology can begin in mid-life, it is still several years from mid-life to when one would develop late-onset aMCI/AD; thus decades-long studies are needed to better understand brain changes in mid-life and how they relate to late-life AD. Therefore, the literature is sparse and generally relies on AD risk (e.g., *APOE* status or family history of AD) to examine memory and neuroimaging in mid-life. Second, many studies with an aging focus examine a memory composite (e.g., averaging learning, delayed recall, and recognition measures) and thus it is difficult to discern the association between delayed recall versus recognition and brain integrity from these studies. Even older-adult studies often do not specifically examine recognition memory as again they either examine aMCI diagnosis, which in the older adult literature does not necessarily imply recognition impairment, or a memory domain. Third, given the AD focus of middle-aging studies, many middle-aging studies focus on the medial temporal lobe and do not explore other regions such as the basal ganglia or the prefrontal cortex.

From the sparse middle-aging research that examines both memory and neuroimaging, there is some indication that memory is associated with several neuroimaging correlates, most notably the medial temporal lobe. For example, the Wisconsin Registry for Alzheimer's Prevention (WRAP) study, which focuses on adults aged 40-65 (mean age = 54) and is enriched with a family history of AD, has reported memory and neuroimaging associations. For example,

in a study of 261 WRAP participants, those with subjective memory complaints had significant cortical thinning in the entorhinal, fusiform, posterior cingulate, and inferior parietal cortices and reduced amygdala volume compared to participants without subjective memory complaints. Subjective memory complaints were also associated with worse verbal memory (Schultz et al., 2015). In 109 participants in the WRAP study, participants that were Aβ+, determined via PET imaging, exhibited significantly thinner entorhinal cortex, accelerated age-associated thinning of the parahippocampal gyrus, and performed worse across cognitive measures, although not significantly worse, compared with the Aβ− group (Doherty et al., 2015). Approximately 65% of WRAP participants were female and approximately 95% of participants were non-Hispanic white. In a study of 210 adults aged 40-59 (mean age = 52, ~70% female, ~90%, non-Hispanic white, and 50% with a family history of dementia) by Ritchie et al. (2017), worse spatial recall and visual recognition as well as greater dementia risk were associated with lower brain and hippocampal volume.

Overall, the middle-aging literature is quite limited, so it is difficult to discern if episodic memory, regardless of the type of memory (e.g., delayed recall and recognition), reliably associates with the medial temporal lobe in middle age. While it is significant that these studies do find associations between memory, AD risk, and the medial temporal lobe (entorhinal cortex, parahippocampal gyrus, and hippocampal volume) as well as other brain structures, these studies do not report prefrontal involvement like that observed in the current study. Of note, the study participants in these two studies markedly differ from the CHARTER cohort; the CHARTER cohort was not enriched for family history of AD, is predominantly male (i.e., 85% in this subsample), and this subsample is 50.5% African American/Black and 38.4% non-Hispanic White. However, Jak et al., (2015), which examined men in their 50s (race/ethnicity breakdown

not stated), also found that MCI diagnosis was associated with smaller hippocampal volume, although only the hippocampus was examined in this study.

One curious finding was that the post hoc analyses examining a subsample of participants showed that better delayed recall was associated with a thinner entorhinal cortex. The aim of these analyses were to examine and confirm that prior findings are applicable to participants that were ideally treated for HIV disease and did not have any current substance use that could confound results. Although it should be noted that full sample is already a group that somewhat differs from the general population of PWH in that this group excludes PWH with severe comorbid conditions, they have little to no current substance use, and are relatively well treated for HIV as compared to the general population (e.g., 72.7% undetectable in this sample as compared to the estimated 56.8% of all PWH in the United States in 2019; Center for Disease Control and Prevention, 2019). Nevertheless, this finding is opposite of what was hypothesized based on the literature. While thicker cortex has been associated with cognitive dysfunction in some settings, suggesting that it is the deviation from normal cortical thickness that is meaningful (Medina et al., 2009), within the HIV and AD literature this has not been observed. In HAND (Alakkas et al., 2019; Ances & Hammoud, 2014; Nichols et al., 2019; Pfefferbaum et al., 2014) and AD (Zhou et al., 2016), atrophy is consistently related to worse cognitive functioning. Therefore, it is likely that this is a spurious finding. Given that this is a relatively small subsample (n=62) and may not be generalizable, and thus this finding should not be over-interpreted.

4.1.2 The neuroanatomical correlates of processing speed and psychomotor skills.

To further validate the specificity of memory and medial temporal lobe relationships and show that memory is not just related to overall brain integrity, processing speed and psychomotor

skills were also examined in aim 1c. It was hypothesized that these two domains would be more associated with fronto-striatal structures implicated in HAND. In the entire sample, processing speed and psychomotor skills were not significantly associated with the medial temporal lobe as hypothesized. However, they were not significantly associated with prefrontal or basal ganglia structures either. Overall, these findings were not in line with the hypotheses, and given that episodic memory was not associated with medial temporal lobes, these findings do not help to demonstrate that associations with the medial temporal lobe are specific to memory and not cognitive functioning in general. In post hoc analyses, a thinner pars orbitalis was significantly associated with worse psychomotor functioning, which was somewhat in line with the hypotheses; however, the literature would suggest that we may expect psychomotor function to be more related to basal ganglia structures, particularly the putamen (Paul et al., 2008; Wright et al., 2016).

4.1.3 Episodic memory was not associated with the primary motor cortex. Lastly, recognition and delayed recall and their association with the primary motor cortex were examined in aim 1d. It was hypothesized that memory would be at least less associated with the motor cortex given that the primary motor cortex is spared in AD. The sub aim was explored in order to complete double dissociation. Consistent with this hypothesis, episodic memory was not significantly associated with the prefrontal cortex. However, given that memory was not associated with the medial temporal lobe, this lack of an association is not meaningful and double dissociation was not supported.

4.1.4 Discussion of AIDs status and *APOE* genotype covariates. When examining covariates for this aim of the study, AIDS status and *APOE* ε4 status were associated with worse delayed recall. Regarding AIDS status, nadir CD4 count has repeatedly been associated with risk

of HAND both within the CHARTER cohort (Heaton et al., 2011) and in other cohorts around the world (McCombe et al., 2013; Njamnshi et al., 2009; Wang et al., 2020). While nadir CD4 count was examined as a potential covariate and was not found to be associated with delayed recall, AIDS status is of course associated with nadir CD4 given that an AIDS diagnosis is defined by either an opportunistic infection or if CD4 cell count drops below 200 cells per milliliter of blood at any point in one's life (Centers for Disease Control and Prevention, 2021). It is thought that greater immunosuppression is associated with CNS injury and those neurologic consequences may persist even after treatment with ART and immune recovery (Heaton et al., 2011; Wang et al., 2020); this highlights the importance of HIV identification and initiation of ART to avoid immunosuppression. Based on the estimated duration of HIV, most of these participants contracted HIV either before ART was available or in the era in which ART was not recommended to be initiated until after immunosuppression. This cohort on average is characterized by a history of immunosupression with immune recovery given that there is high rates of AIDS with evidence of immune recovery as evidenced by a median CD4 count of almost 500 and high rates of current ART use. Given that ART policies have changed and it is now recommended that ART is initiated immediately after diagnosis (Centers for Disease Control and Prevention, 2021), continued research on aging with HIV will be needed to understand different cohort effects (e.g., "survivor bias").

Nadir CD4 has been associated with thinner cortex and smaller brain volumes throughout the brain, particularly in the parietal, temporal, and frontal lobes, and the hippocampus (Cohen et al., 2010; Hassanzadeh-Behbahani et al., 2020). Therefore, it is important to reiterate that episodic memory and prefrontal regions were significantly associated with one another even when accounting for AIDS status. Interestingly, one study found that low nadir CD4 was

associated with reduced functional connectivity in the memory networks (i.e., the Papez circuit) in *APOE* ε4 carriers not but non-carriers (Yang et al., 2021).

Regarding *APOE* status, several studies have examined the association between memory and *APOE* status in middle age, finding that *APOE* ε4 carriers have similar memory and cognitive performance to non-carriers until the mid-to-late 50s when differences start to appear (Lancaster et al., 2017; Zimmerman et al., 2022). Interestingly, the association between *APOE* ε4 status and worse memory, specifically delayed recall but not recognition, was found within this group of PWH whose mean age was in the early 50s. However, other early markers associated with preclinical AD, such as the association between memory and medial temporal lobe structures were not, although *APOE* by medial temporal lobe interactions were not explored. Previous HIV studies have shown mixed results when examining the association between *APOE* status and cognition within PWH. Within the larger CHARTER cohort, Morgan et al. (2013) found that *APOE* ε4 status was not associated with a greater risk of HAND; however, this study was from an earlier timepoint in which participants were, on average, 44.1 years old. Moreover, in another CHARTER study by Cooley et al. (2016) in a sub-sample of CHARTER participants aged 50 and over, *APOE* ε4 status was not associated with volumetric differences on MRI (i.e., total gray and white matter, subcortical gray matter, abnormal white matter, ventricles, sulcal CSF, cerebellar gray and white matter, and cerebellar CSF) or MR spectroscopy (MRS) metabolite analyses. However, these structural analyses may not have had the specificity to detect more minute differences in specific regions of the brain such as the medial temporal lobe.

Nevertheless, the HIV literature is mixed as a review found that some HIV studies do find worse cognitive and brain integrity in PWH who are *APOE* ε4 carriers whereas others do not (Geffin & McCarthy, 2018). Several HIV studies, particularly in PWH over the age of 50,

have found that *APOE* ε4 status is associated with worse brain integrity in several regions including cerebral white matter, the thalamus, and temporal, parietal, and frontal regions. Additionally, one study comparing PWH to HIV-negative controls found *APOE* ε4 carrier status to be beneficial in younger age, consistent with the well-documented antagonistic pleiotropy effect of *APOE* across the lifespan*,* but found that the negative effect of *APOE* ε4 status in persons over the age of 50 was stronger in PWH compared to HIV-negative participants (Chang et al., 2011). Despite this one study, few studies have examined if there is a synergistic effect between *APOE* status and HIV status on cognition and brain integrity, although animal models do suggest possible mechanisms of a synergistic interaction between HIV and *APOE* status (Geffin & McCarthy, 2018).

Notably missing from the HIV literature is an examination of differential associations by sex or race/ethnicity and *APOE*'s association with cognition and brain integrity. In a meta-analysis of aging research studies, *APOE* ε4 women were found to be at greater risk of AD compared to *APOE* ε4 men but only between the ages of 65 and 75 (Neu et al., 2017). Additionally, there are known differential effects of *APOE* status on AD risk by race. The effect of *APOE* status on AD risk is significantly attenuated in African Americans/Black people compared to non-Hispanic white people (Qin et al., 2021). Therefore, future examination of the relationship between sex, race/ethnicity, *APOE* status, and other genetic markers (e.g., *ABCA7*) of AD risk within PWH is certainly warranted.

4.1.5 Summary of Aim 1. In summary, considering the HIV literature, the middle-aging literature, and the finding that episodic memory was associated with prefrontal structures rather than medial temporal lobe structures, episodic memory in middle-aged PWH is more likely related to frontally mediated etiologies. This could indicate that memory in middle-aged PWH is

associated with HIV disease. Notably, this association was seen in PWH on ART without a detectable viral load, showing that this association is seen even in PWH who are virally suppressed. However, it is of course difficult to differentiate between the effect of HIV itself versus the effect of comorbid conditions, many of which may be increased in PWH (although more limited in this sample due to exclusionary criteria) due to the downstream effects of HIV and ART, or a combination of the two. The medial temporal lobe was not associated with episodic memory, which overall may indicate that at this age range, preclinical AD is not likely a contributor to memory functioning. However, the middle-aging literature does not provide a good estimate of when, on average, to expect to start detecting differences, even small, in memory and medial temporal structures in those that are on an AD trajectory; therefore, it is possible that this group is too young to even start detecting any preclinical AD effect. This is further complicated because the middle-aging literature is demographically different from the CHARTER sample, thus highlighting the need for more diverse aging studies. Additionally, this study did not specifically examine differences in the associations between memory and brain structures by AD risk (e.g., family history, *APOE* status); thus, future research should examine memory associations by AD risk, particularly given that *APOE* status was associated with delayed recall. Relatedly, these findings show that *on average* this group is not showing associations with memory and the medial temporal lobe and early signs of preclinical AD, but this does not mean that no participants are on an AD trajectory. In fact, given base rates, some of this group will eventually develop AD.

4.2 Baseline Medial Temporal Lobe Integrity was not Associated with Memory Decline

The second primary aim of this study was to examine if baseline medial temporal lobe structures were associated with change in memory over time. It was hypothesized the smaller (hippocampal volumes) or thinner (entorhinal cortex and parahippocampal gyrus) medial temporal lobe structures would be associated with decline in recognition and delayed recall.

4.2.1 Variable recognition impairment status across visits. First, the multi-level models examining the cross-level interactions between time and medial temporal structures with dichotomous recognition as the outcome did not converge. This analysis would have examined if baseline medial temporal lobe structures are associated with greater likelihood of impaired recognition over time. Given that the models did not converge, this indicates the models were overparameterized and that the model was not supported by the data. This was possibly affected by the modest sample size, with a particularly small (n=12) group of participants with impaired recognition at baseline.

Examining the variability in recognition over time within this study is still meaningful. For example, of the 12 participants that were impaired at baseline, only two remained impaired. Moreover, in those that were not impaired at baseline but were impaired at some point in time, most reverted back to unimpaired at subsequent visits. Only four participants remained impaired in recognition over time, although with limited follow-up. There is not data on why these participants do not have additional follow-up (e.g., lost contact, moved, deceased, too impaired or sick to continue in the study), and thus it is hard to make any definitive conclusion as to if consistently impaired recognition is a risk factor for negative outcomes. However, it would certainly be warranted to examine if consistent recognition impairment is associated with negative outcomes in a larger group of middle-aged and older PWH. For example, this small

group of participants that were consistently impaired in recognition memory could represent those that are progressively declining and are on more of an AD trajectory. Moreover, a better understanding of how those that are consistently impaired differ (e.g., demographics, comorbid conditions) from those that revert to unimpaired recognition would be beneficial.

There are multiple reasons that may explain why recognition impairment status was variable over time. First, HIV-associated neurocognitive impairments are known to fluctuate over time. For example, in the CHARTER study, 17% of the sample improved over time (Heaton et al., 2015). Therefore, this could simply reflect the heterogeneous and fluctuating course of HAND over time. Second, recognition is sometimes used as an embedded performance validity measure. While all participants were administered a standalone performance validity test at the beginning of the neuropsychological evaluation to verify credible test performance, effort can fluctuate throughout testing. That said, none of the participants at baseline were below the proposed cut-off of ≤5 for HVLT-R recognition (Bailey et al., 2018; Sawyer et al., 2017), making this explanation less likely. Lastly, this variability over time may be in part due to the psychometric properties of the HVLT-R and the BVMT-R. Recognition for both the BVMT-R and the HVLT-R are skewed with known ceiling effects, meaning that there is limited variability in this variable (Benedict, 1997; Benedict et al., 1998). Therefore, a one- or two-point difference can result in large differences in the normative score. Moreover, there are known modest inter-form differences on the HVLT-R recognition (Benedict et al., 1998). Additionally, while the HVLT-R and BVMT-R test-retest reliability of recognition show adequate test-retest stability coefficients, the test-retest reliability of recognition is less reliable than other test measures such as total learning or delayed recall (Benedict et al., 1998; Benedict et al., 1996; Strauss et al., 2006; Woods et al., 2005).

4.2.2 Baseline medial temporal lobe integrity was not associated with longitudinal delayed recall. Next, longitudinal delayed recall was examined. Most notably, there was little decline in delayed recall over time; the delayed recall T-score decreased by 0.041 per year. Additionally, there was little variability in this slope given that the standard deviation of the slope was 0.678. None of the cross-level interactions between medial temporal lobe structures and years since baseline were significant indicating that medial temporal lobe structures at baseline were not associated with a change in delayed recall. However, given that there was little variability in delayed recall over time, this was not surprising.

As discussed in the introduction, worse baseline medial temporal lobe structures, particularly the hippocampus and entorhinal cortex, have been associated with an increased risk of future AD, MCI, and decline in cognition in older adults without HIV (Bangen et al., 2018; Gorbach et al., 2017; Pini et al., 2016). This relationship is less understood in middle age. One study by Gorbach et al. (2017) found that hippocampal atrophy was associated with a decline in episodic memory in adults over the age of 65 but not in middle-aged adults between the ages of 55 to 60. As highlighted above, it is possible that the cohort from the current study is too young to expect to see associations between medial temporal lobe structures and longitudinal memory.

Importantly, the current study only examined cross-sectional structural MRI; therefore, we cannot assume that smaller or thinner medial temporal lobe structures are indicative of atrophy. Additionally, this study does not have an HIV-negative comparison group and did not use normatively-adjusted morphometric values (e.g., NOMIS; Potvin et al., 2022), so it is unclear if participants in this cohort deviate from average, although accelerated brain atrophy has been demonstrated in PWH previously (Pfefferbaum et al., 2014). Therefore, research examining changes in the medial temporal lobe and how that change relates to episodic memory,

particularly recognition memory, in persons with and without HIV over the age of 65 is needed. This research may help to better understand if medial temporal lobe structures are associated with the risk of an AD trajectory and if these associations differ by HIV-serostatus.

While there may be some individuals in this group that are experiencing objective decline, on average, in this group of middle-aged PWH we did not observe a decline in delayed recall T-scores over time. These T-scores are age-corrected, so the raw scores on the tests may be declining but they are not declining at a rate greater than what would be expected for age. Additionally, these T-scores also account for practice effects, which if unaccounted for can mask decline, although the best method of practice-effect correction is still debated (Vivot et al., 2016). Similar results showing stable cognition over time were found in a study by Saloner et al. (2022) in a larger sample of CHARTER participants aged 50 and over. This study employed growth mixture modeling, and none of the three latent classes demonstrated a decline in global T-score over time. However, other studies of PWH over the age of 50 have observed a greater than expected effect of aging on episodic memory (e.g., in the Multicenter AIDS Cohort Study, Goodkin et al., 2017) and a recent systematic review found accelerated neurocognitive aging in 75% of longitudinal studies in PWH (Aung et al., 2020).

Some researchers have questioned if accelerated aging could be due to a neurodegenerative cause such as AD given the high prevalence of risk factors for AD in PWH such as chronic inflammation, increased cardiometabolic comorbidities, and lower brain reserve (Cohen et al., 2015; Rubin et al., 2019b). While emerging studies have demonstrated some possible ways to disentangle HAND and aMCI (e.g., olfaction, memory performance; Lobo et al., 2022; Sundermann et al., 2021a; Sundermann et al., 2021b), it remains unclear if PWH are at increased risk of AD or if a neurodegenerative etiology could, at least in part, account for some

of the observed accelerated aging. For example, Milanini et al. (2020) showed a low frequency of amyloid positivity, measured via PET imaging, among virally suppressed PWH over the age of 60, and the rates of amyloid positivity were similar to published rates among an age-matched seronegative sample. However, a recent study among Medicare enrollees did find a higher prevalence of AD and related disorders among PWH (Yu et al., 2022).

4.2.3 Summary of Aim 2. In summary, this aim showed that recognition was variable over time. While amnestic decline could not specifically be tested given that recognition models did not converge, these analyses indicated that within this group, medial temporal lobe integrity was not associated with a decline in delayed recall over time. Additionally, delayed recall only marginally declined over time (i.e., <0.1 T-score per year), thus adding to the mixed literature examining episodic memory in middle-aged and older PWH. Overall, this study did not detect clear signs of preclinical AD in this group, as delayed recall did not change over time and baseline measures of medial temporal lobe integrity were not associated with memory over time as seen in HIV-negative older adults. However, it is not clear if these associations would be expected in a middle-aged cohort of PWH due to a lack of literature on this topic in middle-aged adults. Therefore, it would be beneficial to re-examine this analysis in an older cohort of PWH.

4.3 Examining if the Medial Temporal Lobe Mediates a Relationship Between Peripheral Inflammation and Episodic Memory

The last aim of this study was to examine if the medial temporal lobe mediates a relationship between peripheral inflammation and memory. It was hypothesized that medial temporal lobe structures would mediate a relationship between peripheral inflammation and episodic memory. Five peripheral biomarkers of inflammation were examined (i.e., IL-6, TNF-α, CCL2, CRP, and CXCL10), and these biomarkers were chosen given that they have been

associated with cognition in AD and HIV. In this mediation model, the association between peripheral biomarkers of inflammation and medial temporal lobe structures was also explored and the relationship between medial temporal lobe structures and memory was also reported, although this second relationship was already explored in aim 1.

First, the mediation models examining recognition indicated poor model fit. Therefore, the relationship between the five plasma biomarkers of inflammation and recognition was examined instead. Greater levels of plasma CRP were associated with lower odds of having impaired recognition. None of the other plasma biomarkers of inflammation were associated with recognition impairment. These findings are generally not in line with the HAND (Williams et al., 2020a), middle-aging (Marsland et al., 2015), or older adult literature (Shen et al., 2019; Su et al., 2019). Aging and HIV studies have found that a greater concentration of these plasma biomarkers of inflammation are associated with greater risk of HAND, worse memory, and an increased risk of future development of MCI or AD. However, many of these studies only find weak associations, and these studies do not examine recognition memory. The current study had a very small sample of PWH with impaired recognition; thus, it is possible that the CRP finding is spurious, and this finding should not be over-interpreted. Therefore, analyses should be re-examined in a larger, more generalizable sample.

Next, a single-mediator model was used to examine if medial temporal lobe structures mediate the relationship between plasma biomarkers of inflammation and delayed recall. In the entire sample, none of the plasma biomarkers of inflammation were significantly associated with any of the medial temporal lobe structures, there were no significant direct effects between the plasma biomarkers of inflammation and delayed recall, and no mediated effect was established. As stated above, the lack of association between inflammation and delayed recall is a little

surprising given that the association between inflammation and worse cognition has been demonstrated in HAND and the aging literature. Although, the effect sizes are often small, and the middle-aging literature is limited.

Additionally, some of the peripheral inflammatory markers examined in this study (i.e., CRP and IL-6) have been associated with medial temporal lobe integrity and function in older adults (Anan et al., 2011; Bettcher et al., 2012; Warren et al., 2018), but the association between inflammation and the medial temporal lobe is much less studied in mid-life and PWH. Marsland et al., 2015 did find that IL-6 and CRP were associated with worse memory and smaller hippocampal volumes in middle-aged adults; however, it was cortical grey matter volume, not the hippocampus, that mediated the relationship between inflammation and memory. Studies in adults with HIV have found that peripheral biomarkers of immune activation (i.e., sCD14, sCD163, and NGAL) but not biomarkers examined in this study (i.e., CCL2, IL-6, and CRP) were associated with frontal and temporal lobe regions (Kamkwalala et al., 2020; Williams et al., 2020b). Interestingly, in post hoc analyses examining participants on ART who were virally suppressed, greater CRP was associated with a thinner parahippocampal gyrus. This finding may be in line with the Marsland et al., 2015 study. However, the current study had a small sample size, and several analyses were examined in post hoc analyses without accounting for multiple comparisons, so this finding should be interpreted cautiously.

Integrating the aging and HIV literature, it is unclear if the association between peripheral inflammation, medial temporal lobe, and episodic memory is consistently observed in mid-life. While the best method of determining the necessary sample size to detect a mediation effect is debated, it is still likely this study's modest sample size of 92 is underpowered to detect a mediation effect, particularly given that large effect sizes were not expected (Schoemann et al.,

2017; Sim et al., 2022). Therefore, the role of inflammation and its association with brain integrity (i.e., the medial temporal lobe and the frontal lobe given the HIV literature) and episodic memory in PWH should continue to be examined, particularly in larger samples with greater power to detect these associations. It will be particularly important to examine these relationships in PWH aged 65 and over given that this is the age range in which these associations between inflammation, memory, and MCI/AD risk are more consistently found.

One thing to note is that these peripheral inflammatory biomarkers were examined separately, as each biomarker may have a different relationship with memory and brain integrity. There is currently no "gold-standard" way to combine inflammation biomarkers into a single composite. However, some researchers have examined inflammation composites (Montoya et al., 2019; Walker et al., 2017). Therefore, future studies may want to examine a wider array of biomarkers and employ an inflammation composite, particularly given that the impact of inflammation on brain integrity and memory may be due to the compounding effects of multiple inflammatory biomarkers. Additionally, these biomarkers were only examined at one timepoint, so a better understanding of how changes in these inflammatory biomarkers over time are associated with brain integrity and cognition is also needed.

Lastly, this study examined peripheral inflammation. Peripheral inflammation is easier to assess more non-invasively (i.e., with a routine blood draw) in comparison to a lumbar puncture which is needed to collect CSF (Williams et al., 2020a). However, peripheral inflammation may not be as reflective of neuroinflammation compared to CSF biomarkers. Although, some studies have shown that plasma inflammation may be more associated with cognition (Burdo et al., 2013). Thus, future studies should ideally examine both plasma and CSF biomarkers to determine if examining peripheral inflammation is sufficient. Ultimately, a better understanding

of the role of inflammation and the most efficient way to measure it could help to inform interventions that could lower inflammation (e.g., lifestyle factors, pharmaceuticals) in PWH, if future research indicates that lowering inflammation may be cognitively beneficial.

4.4 Limitations and Future Directions

In addition to the limitations discussed above, there are additional limitations that should be considered. First, the generalizability of the sample should be considered. As noted several times in the discussion, the age range (i.e., mean age = 51.4 years; range = 45 – 68) may be too young to expect a significant number of participants to have started to accumulate AD pathology. Additionally, the sample was predominantly male (i.e., 85.7%), which is somewhat reflective of the current demographics of PWH in the United States (Centers for Disease Control and Prevention, 2017). Nevertheless, there are known sex differences in HIV, AD, and inflammation (Milan-Mattos et al., 2019; Royal III et al., 2016) that this project is underpowered to test but should be further examined in future studies. For example, women living with HIV are at greater risk of neurocognitive impairment, particularly in the domains of memory, speed of information processing, and motor function potentially due to a difference in psychosocial factors (e.g., access to care, stigma, SES), comorbid conditions (e.g., mental health and substance use disorders), and biological factors (e.g., inflammation, hormonal, genetic; Rubin et al., 2019a). It is also known that women are at greater risk of AD (Mazure & Swendsen, 2016).

Additionally, participants with severe confounding comorbid conditions (as defined in the Methods section) were excluded from this study, and this sample was characterized by relatively low current drug use and relatively high ART use. These factors are also known to impact cognitive and brain functioning; for example, cannabis use has been associated with

better cognitive functioning and lower inflammation in PWH (Watson et al., 2021; Watson et al., 2020). As the HIV population continues to age, it will be important to understand if there are any associations between these sociodemographic variables and AD risk that str specific to PWH.

Related to generalizability, one odd finding was the higher-than-expected number of participants with the *APOE* ε2 allele. The percentage of participants with at least one ε4 allele (29.5%; 17.6% of total alleles) was somewhat comparable to the general population, with estimates ranging from 10% to 25% of people having at least one ε4 allele. Additionally, it is known that Black/African American persons and persons of African ancestry have increased rates of the *APOE* ε4 allele compared to non-Hispanic White people or those of European descent (Troutwine et al., 2022; Weuve et al., 2018). Indeed, the CHARTER study has found an increased prevalence of the ε4 allele in Black/African American participants as compared to non-Hispanic White participants (Cooley et al., 2016). The *APOE* ε2 allele is much less studied because it is more rare, but having an *APOE* ε2 allele is associated with a lower-than-average risk of AD. In this study, the percentage of participants with at least one *APOE* ε2 allele (26.1%; 14.2% of total alleles) was higher than the general population (estimates range from 3% to 10% of people having at least one ε2 allele; Huebbe & Rimbach, 2017; Suri et al., 2013). Similar to the *APOE* ε4 allele, the prevalence of *APOE* ε2 is known to vary by ancestorial continent and latitude. The *APOE* ε2 allele penetrance is 9.9% in Africa, which is higher than the *APOE* ε2 allele penetrance in Europe (Huebbe & Rimbach, 2017; Suri et al., 2013).

Even accounting for these demographic differences, the prevalence of the *APOE* ε2 is high, and this overrepresentation of the *APOE* ε2 allele may mean this group is, on average, at decreased risk of AD. This increased prevalence could be due to a selection bias (e.g., those that were doing better cognitively were more likely to be eligible for and interested in the study).

Information on the *APOE* ε2 in PWH is very limited, but more research is certainly needed to understand AD risk in diverse groups of PWH. One minor point is that four participants with the *APOE* ε24 genotype were categorized as *APOE* ε4-. The limited literature on this genotype does suggest a somewhat elevated risk of AD associated with this genotype, but much less than that of those that are *APOE* ε34 or *APOE* ε44 (Rasmussen et al., 2018). Therefore, the *APOE* ε24 participants were categorized as *APOE* ε4- given the only slightly elevated risk. Other categorizations could be explored, although given the small number of participants that are *APOE* ε24 it is unlikely to make a significant difference.

In addition to the potentially limited generalizability due to the demographics and clinical characteristics of this sample, this study examined a relatively modest sample size. A sample size of 92 is not necessarily small compared to other imaging studies. However, as highlighted throughout this discussion, this modest sample size could still limit the power to detect associations. Future studies in this area would benefit from improving statistical power either by enrolling a larger overall sample and/or recruiting participants with memory impairment, particularly recognition impairment.

This study is also limited in that it does not include an HIV-negative comparison group. Utilizing preexisting CHARTER data allowed for longitudinal analysis over 12 years and the ability to efficiently examine the neuroanatomical correlates of memory in middle-aged and older PWH. However, this study is therefore limited by pre-defined CHARTER protocol and design. Specifically, CHARTER did not enroll HIV-negative comparison participants, which precludes examination of how the relationship between memory profiles and brain integrity differ by HIV serostatus. While there is ample HIV-negative middle-aging literature to compare these results to, many of these HIV-negative middle-aging studies are demographically (e.g.,

higher education and larger percentages of non-Hispanic white participants) and psychosocially different than this group. However, even with a good comparison group, it is difficult to discern the effect of HIV versus the neurotoxic effects of ART and the downstream consequences of ART (e.g., metabolic syndrome). Nevertheless, future studies would benefit from a demographically and psychosocially similar HIV-negative group to better understand if the associations between memory and neuroimaging correlates are specific to PWH or if these are associations seen regardless of HIV status.

In the current study, delayed recall and recognition were examined separately rather than dichotomously splitting participants into aMCI versus non-aMCI groups (e.g., using adapted Jak/Bondi criteria) or comparing HAND versus aMCI groups as in Sundermann et al. (2021a). Examining recognition and delayed recall was a critical first step to inform future diagnostic improvements. Additionally, examining delayed recall continuously was advantageous because it increases variability and more subtle differences observed in mid-life may not be captured by diagnostic cut-points. However, associations between biological markers associated with AD (e.g., olfactory dysfunction, elevated rates of $A\beta_{42}$ plaques) have been found in PWH using aMCI criteria (Sundermann et al., 2021a; Sundermann et al., 2021b). Therefore, data could be re-examined using adapted aMCI criteria and HAND criteria to examine if a more comprehensive approach to examining episodic memory (i.e., aMCI) is more sensitive to the medial temporal lobe than examining delayed recall and recognition separately.

As described in the Methods section, the differences in scanner by site was corrected by regressing scanner from the data. Accounting for scanner was necessary given that prior CHARTER studies have shown that pooling MRI data from multiple sites is feasible, but there are documented differences between the scanners (Fennema-Notestine et al., 2007; Jernigan et

al., 2011). However, accounting for scanner is essentially accounting for study site, which is somewhat problematic given that study site has been shown to be associated with the risk of neurocognitive impairment in the CHARTER study. For example, Marquine et al. (2018) found a significant effect of study site, specifically when comparing New York and San Diego, on the risk of neurocognitive impairment that was not fully accounted for by race/ethnicity differences. It is thought that differences in the risk of neurocognitive impairment are likely due to psychosocial and environmental factors that are associated with geographic location (e.g., access to care, educational quality, stigma, environmental pollutants). These psychosocial and environmental factors could also impact brain integrity, and thus accounting for scanner, while necessary, may mask real differences in brain integrity. Therefore, future studies may want to employ a different statistical method that could account for differences in scanner while not eliminating the effect of study site.

Relatedly, future studies could explore alternative ways to analyze the imaging data. For example, *a priori* regions of interest were selected given the interest in focusing on brain structures associated with HAND and aMCI. However, the FreeSurfer processing approaches provide a broad array of additional regions that could also be explored. Furthermore, additional data-driven analytic approaches exist such as whole-brain voxel-based morphometry. This study took a hypothesis-driven approach, although examination of other regions of interest, such as subdivisions of the cingulate cortex, could be done in an exploratory fashion. Other imaging modalities such as diffusor tensor imaging to examine white matter integrity, arterial spin labeling to examine cerebral blood flow, MRS to examine neurochemical alterations, and amyloid PET imaging may also help to better understand episodic memory in PWH.

4.5 Summary and Clinical Implications

Despite these limitations, this study has several clinical implications. This study showed that memory in these participants aged 45 to 68 was associated with prefrontal structures but not medial temporal lobe structures. This suggests that episodic memory in middle-aged PWH is more associated with frontally mediated etiologies such as HIV rather than etiologies associated with the medial temporal lobe such as AD. Second, recognition impairment was quite variable over time. Due to this variability over time, recognition may not serve as a good clinical marker to help distinguish aMCI from HAND. However, this group of participants is considerably younger than when late-onset AD presents; therefore, continued research is needed to examine if recognition may be a useful clinical marker to differentiate aMCI and HAND in older age. This study suggests that in middle-aged PWH without severe confounding medical conditions and high rates of ART use, there is not a greater than expected decline in delayed recall. However, more research is needed to more definitively determine if there is accelerated memory decline in middle-aged PWH. Lastly, while there was some indication that peripheral CRP may be associated with memory, overall, most biomarkers of inflammation were not associated with episodic memory and the medial temporal lobe did not mediate a relationship between inflammation and episodic memory. However, given the limitations described above, ongoing research on this topic is needed.

In summary, this study found that memory may be more related to HIV disease than preclinical AD, and delayed recall did not significantly decline over several years. This is positive news given that HIV-associated neurocognitive impairment is usually non-progressive. However, more research is needed in older PWH, when aMCI/AD would be more expected.

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