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Effects of Cannabis Exposure on Neuroinflammation, Neurocognition, and Everyday Function in HIV and Aging

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Watson, Caitlin Wei-Ming

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Effects of Cannabis Exposure on Neuroinflammation, Neurocognition, and Everyday Function in HIV and Aging

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

in

Clinical Psychology

by

Caitlin Wei-Ming Watson

Committee in charge:

University of California San Diego

Professor Igor Grant, Chair
Professor Suzi Hong
Professor Erin Morgan

San Diego State University

Professor Aaron Blashill
Professor Jonathan Helm

2022

The Dissertation of Caitlin Wei-Ming Watson is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

University of California, San Diego
San Diego State University

2022

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS

HIV = human immunodeficiency virus
PWH = people with HIV
PLHIV = people living with HIV
CNS = central nervous system
CSF = cerebrospinal fluid
ART = antiretroviral therapy
AIDS = acquired immunodeficiency syndrome
THC = Δ^9-tetrahydrocannabinol
CBD = cannabidiol
CBG = cannabigerol
CBC = cannabichromene
CBN = cannabinol
IL-6 = interleukin-6
CCL2/MCP-1 = chemokine (C-C motif) ligand 2/monocyte chemoattractant protein-1
CLCX10/IP-10 = C-X-C motif chemokine 10/interferon-gamma-inducible protein-10
sCD14 = soluble cluster of differentiation 14
sTNFR-II = soluble tumor necrosis factor receptor type II
TNF-α = tumor necrosis factor-alpha
MIP-1α = macrophage inflammatory protein-1α
IL-1β = interleukin-1β
IL-8 = interleukin-8/neutrophil chemotactic factor
NF-κB = nuclear factor-κB

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Chapter 1, in full, is a reprint of the material as it appears in *JAIDS: Journal of Acquired Immune Deficiency Syndromes* 2020. Watson, C. Wei-Ming, Paolillo, Emily W., Morgan, Erin E., Umlauf, Anya, Sundermann, Erin E., Ellis, Ron J., Letendre, Scott, Marcotte, Tom D., Heaton, Robert K., & Grant, Igor. The dissertation author was the primary investigator and author of this paper.

Chapter 2, in full, is a reprint of the material as it appears in *JINS: Journal of the International Neuropsychological Society* 2021. Watson, C. Wei-Ming, Campbell, Laura M., Sun-Suslow, Ni, Hong, Suzi, Umlauf, Anya, Ellis, Ron J., Iudicello, Jennifer E., Letendre, Scott, Marcotte, Tom D., Heaton, Robert K., Morgan, Erin E., & Grant, Igor. The dissertation author was the primary investigator and author of this paper.

Chapter 3, in part, is currently under review for publication of the material. Watson, C. Wei-Ming, Sundermann, Erin E., Helm, Jonathan, Paolillo, Emily, W., Ellis, Ron J., Letendre, Scott, Marcotte, Tom D., Heaton, Robert K., Morgan, Erin E., & Grant, Igor. The dissertation author was the primary investigator and author of this paper.

VITA

EDUCATION

2016-2022 Ph.D. in Clinical Psychology
San Diego State University/University of California San Diego
Major Area of Study: Neuropsychology
San Diego, CA

2016-2018 M.S. in Clinical Psychology
San Diego State University
San Diego, CA

2009-2013 B.A. in Psychology and Urban Studies
Columbia University
New York, NY

GRANTS, ACADEMIC AWARDS, AND HONORS

2016-2021 T32 Predoctoral Fellowship Training in Research on Addictions and Interdisciplinary NeuroAIDS, National Institute on Drug Abuse (NIDA)
Training Director: Robert K. Heaton (T32 DA031098)
2021 Local P.E.O. Award, San Diego Chapter
2020 Trainee Champion of Diversity Award, UC San Diego Psychiatry Department
2018 Multi-Modal Imaging of Racial Discrimination across the Lifespan, National Science Foundation (NSF) Graduate Research Fellowship Program Honorable Mention
2018 Complicated Grief Therapy Training Scholarship, UC San Diego Psychiatry Department
2018-2021 First-author Publication Awards, SDSU/UC San Diego JDP
2016-2021 Conference Travel Awards, SDSU/UC San Diego JDP
2013 Graduated *cum laude* (top 25% of class), Columbia University
2012-2013 Senior Thesis Grant Award, Columbia University
2011 New York Academy of Medicine Fellowship, Columbia University
2009-2013 Dean's List, Columbia University
2009-2013 Urbanek-Levy Education Fund Scholarship, KLA-Tencor

PEER-REVIEWED PUBLICATIONS

1. **Watson, C. W.-M.**, Kamalyan, L., Tang, B., Hussain, M. A., Cherner, M., Rivera Mindt, M., Byrd, D. A., Franklin, D., Collier, A. C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., McCutchan, J. A., Ellis, R. J., Grant, I., Heaton, R. K., & Marquine, M.J. for the CHARTER group. (2022) Ethnic/racial disparities in longitudinal neurocognitive decline in people with HIV. *Journal of Acquired Immune Deficiency Syndromes, 90*(1), 97-105. doi: 10.1097/QAI.0000000000002922

2. Angevaare, M. J., Vonk, J. M., Bertola, L., Zahodne, L., **Watson, C.W-M**., Boehme, A., Schupf, N., Mayeux, R., Geerlings, M. I., & Manly, J.J. (2022) Predictors of incident mild cognitive impairment and its course in a diverse community-based population. *Neurology, 98*(1), e15-e26. doi: 10.1212/WNL.0000000000013017

3. Paolillo, E. W., Saloner, R., Kohli, M., **Watson, C. W.-M.**, Moore, R. C., Heaton, R. K., & Moore, D. J. (2021) Binge drinking relates to worse neurocognitive functioning among adults aging with HIV. *Journal of the International Neuropsychological Society*, 1-11. Epub. doi: 10.1017/S1355617721000783

4. **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 Special Issue: Clarifying the Complexities of Cannabis and Cognition, 27*(6), 661-672. doi: 10.1017/S1355617720001447

5. Morgan, E.E., **Watson, C.W.-M.**, Woods, S.P., Gilbert, P.E., Villalobos, J., & Verduzco, M. (2020) Misattributions of the Source of Health-Related Information in HIV Disease. *Journal of Clinical and Experimental Psychology, 43*(1), 1-14. doi: 10.1080/13803395.2020.1851355

6. **Watson, C. W.-M.**, Pasipanodya, E., Savin, M. J., Ellorin, E. E., Corado, K. C., Flynn, R. P., Opalo, C., Lampley, E., Henry, B. L., Blumenthal, J. S., Bolan, R., Morris, S., & Moore, D. J. (2020). Barriers and facilitators to PrEP initiation and adherence among transgender and gender non-binary individuals in Southern California. *AIDS Education and Prevention, 32*(6), 472-485. doi: 10.1521/aeap.2020.32.6.472

7. 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

8. Pasipanodya, E. C., Montoya, J. L., **Watson, C. W.-M.,** Marquine, M. J., Hoenigl, M., Garcia, R., Kua, J., Gant, V., Trambley, J., & Moore, D. J. (2020). Tailoring a mobile health text-messaging intervention to promote antiretroviral therapy adherence among African Americans: A qualitative study. *PLoS ONE, 15*(6), e0233217. doi: 10.1371/journal.pone.0233217

9. Saloner, R., Cherner, M., Sundermann, E. E., **Watson, C. W.-M.**, Iudicello, J. E., Letendre, S. L., Kumar, A., & Ellis, R. J. (2020). COMT Val158Met genotype alters the effects of methamphetamine dependence on dopamine and dopamine-related executive function: Preliminary findings. *Psychiatry Research, 292,*113269. doi: 10.1016/j.psychres.2020.113269

10. **Watson, C. W.-M.**, Paolillo, E. W., Morgan, E. E., Umlauf, A., Sundermann, E. E., Ellis, R. J., Letendre, S., Marcotte, T. D., Heaton, R. K, & Grant, I. (2020). Cannabis exposure is associated with a lower likelihood of neurocognitive impairment in people living with HIV. *Journal of Acquired Immune Deficiency Syndromes, 83*(1), 56-64. doi: 10.1097/QAI.0000000000002211

11. Papapanou, P. N., Park, H., Cheng, B., Kokaras, A., Paster, B., Burkett, S., **Watson, C. W.-M**., Annavajhala, M. K., Uhlemann, A. C., & Noble, J. M. (2020). Subgingival microbiome and clinical periodontal status in an elderly cohort: The WHICAP ancillary study of oral health. *Journal of Periodontology*, 1-12. doi: 10.1002/JPER.20-0194

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13. Bertola, L., **Watson, C. W.-M.**, Avila, J. F., Zahodne, L. B., Angevaare, M. J., Schupf, N. S., & Manly, J. J. (2019). Predictors of episodic memory performance across educational strata: Multiple-group comparisons. *Journal of the International Neuropsychological Society, 25*(9), 901-909. doi: 10.1017/S1355617719000717

14. Deiss, R., Campbell, J., **Watson, C. W.-M.,** Moore, R. C., Crum-Cianflone, N. F., Wang, X., Letendre, S., Maves, R. C., Ganesan, A., Okulicz, J., Moore, D. J., & Agan, B. K. (2019). Posttraumatic stress disorder and neurocognitive impairment in a U.S. military cohort of persons living with HIV. *Psychiatry: Interpersonal and Biological Processes, 82*(3), 228-239. doi: 10.1080/00332747.2019.1586503

15. **Watson, C. W.-M.**, Sundermann, E. E., Hussain M. A., Umlauf, A., Thames, A. D., Letendre, S. L., Moore, R. C., Jeste, D. V., Morgan, E. E., & Moore D. J. (2019). Effects of trauma, economic hardship, and stress on neurocognition and everyday functioning outcomes in HIV. *Health Psychology, 38*(1), 33-42. doi: 10.1037/hea0000688

16. Alakkas, A., Ellis, R. J., **Watson, C. W.-M.**, Umlauf, A., Heaton, R. K., Letendre, S., Collier, A., Marra, C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., Simpson, D., McCutchan, J. A., Kallianpur, A., Gianella, S., Marcotte, T., Grant, I., & Fennema-Notestine, C. for the CHARTER Group. (2018). White matter damage, neuroinflammation, and neuronal integrity in HAND. *Journal of Neurovirology, 25*(1), 32-41. doi: 10.1007/s13365-018-0682-9

17. Shariff, J. A., Burkett, S., **Watson, C. W.-M.**, Cheng, B., Noble, J. M, & Papapanou, P. N. (2018). Periodontal status among elderly inhabitants of northern Manhattan: the WHICAP ancillary study of oral health. *The Journal of Clinical Periodontology, 45*(8), 909-919. doi: 10.1111/jcpe.12927

18. Moore, R. C., Hussain, M. A., **Watson, C. W.-M.**, Fazeli, P. L., Marquine, M. J., Yarns, B. C., Jeste, D. V., & Moore, D. J. (2018). Grit is associated with better neurocognitive and everyday functioning among adults living with HIV. *AIDS and Behavior, 22*(10), 3214-3225. doi: 10.1007/s10461-018-2061-1

19. Zahodne, L. B., **Watson, C. W.-M.,** Seehra, S., & Martinez, M. (2017). Positive psychosocial factors and cognition in ethnically diverse older adults. *Journal of the International Neuropsychological Society, 24*(3), 294-304. doi: 10.1017/S1355617717000935

20. **Watson, C.W.-M.**, Manly, J.J. & Zahodne, L.B. (2016). Does bilingualism protect against cognitive aging? Methodological issues in research on bilingualism, cognitive reserve, and dementia incidence. *Linguistic Approaches to Bilingualism: Special Issue on Bilingualism and Executive Function: An interdisciplinary approach*, *6*(5), 590-604. doi: 10.1075/lab.15043.wat [Republished in 2019. *Bilingualism, Executive Function, and Beyond. Questions and Insights*, 2019]

PEER-REVIEWED ABSTRACTS AND ORAL PRESENTATIONS

1. **Watson, C. W.-M.**, Morgan, E. E., Sun-Suslow, N., Letendre, S., Hussain, M. A., Heaton, R.K., Grant, I., & Iudicello, J.E. (2021). *Alexithymia is associated with different patterns of pro-inflammatory and vascular biomarkers in people with HIV and/or methamphetamine dependence*. Poster presented at the 50th annual meeting International Neuropsychological Society, New Orleans, LA.

2. Sun-Suslow, N., **Watson, C. W.-M.**, Iudicello, J. E., Heaton R. K., & Morgan, E. E. (2021, November). *Frailty syndrome is associated with decreased socio-emotional functioning in people with HIV: A NIH Toolbox Emotion Battery study*. Poster presented at the 41st annual meeting of the National Academy of Neuropsychology, Washington D.C.

3. Kohli, M., Kamalyan, L., Saloner, R., **Watson, C.W.M**., Lobo, J., Montoya, J.L., Umlauf, A., Ellis, R.J., Grant, I., & Moore, D.J. (June, 2021). *Effect of lifetime substance use disorders on neuropsychiatric distress among persons with and without HIV.* Poster presented at the 44th annual meeting Research Society on Alcoholism, San Antonio, TX.

4. **Watson, C. W.-M.**, Morgan, E. E., Paolillo, E. W., Ellis, R.J., Letendre, S., & Grant, I. (2021, February). *Cannabis use and 7-year longitudinal cognitive trajectories among older adults*. Paper presented at the 49th annual meeting International Neuropsychological Society, San Diego, CA.

5. Hussain, M. A., **Watson, C. W.-M.**, Morgan, E. E., Iudicello, J. E., Heaton, R. K., Roesch, S. C., Jeste, D. V., & Moore, D. J. (2021, February). *Combined effects of loneliness and inflammation on depression in people with HIV.* Paper presented at the 49th annual meeting International Neuropsychological Society, San Diego, CA.

6. Paolillo, E. W., Saloner, R., **Watson, C. W.-M.**, Ellis, R.J., Letendre, S., Iudicello, J. E., Grant, I., Heaton, R. K., & Moore, D. J. (2021, February). *Higher cumulative depression and plasma d-dimer synergistically predict steeper neurocognitive declines over time among people with HIV*. Paper presented at the 49th annual meeting International Neuropsychological Society, San Diego, CA.

7. Morgan, E. E., Iudicello, J. E., **Watson, C. W.-M.**, Sun-Suslow, N., & Heaton, R. K. (2021, February). *Alexithymia is associated with worse real-world functioning among people with controlled HIV disease*. Poster presented at the 49th annual meeting International Neuropsychological Society, San Diego, CA.

8. Guareña, L. A., Kamalyan, L., Morgan, E. E., **Watson, C. W.-M.**, Umlauf, A., Heaton, R. K, & Marquine, M. J. (2021, February). *Impact of emotional health on cognition amongst Hispanic and Non-Hispanic White people living with HIV*. Poster presented at the 49th annual meeting International Neuropsychological Society, San Diego, CA.

9. Breton, J., Kamalyan, L., Paredes, A. M., **Watson, C. W.-M.**, Cherner, M., Moore, R.C., & Marquine, M. J. (2021, February). *Psychological acculturation and cognition among older Latinos living with and without HIV*. Poster presented at the 49th annual meeting International Neuropsychological Society, San Diego, CA.

10. **Watson, C. W.-M.**, Morgan, E. E., Paolillo, E. W., Ellis, R.J., Letendre, S., & Grant, I. (2020, February). *Recent cannabis use is associated with lower levels of inflammatory chemokines MCP-1 and IP-10 in CSF among people living with HIV*. Poster presented at the 48th annual meeting International Neuropsychological Society, Denver, CO.

11. Saloner, R., Ellis, R. J., Sundermann, E. E., **Watson, C. W.-M.,** Letendre, S. L., Kumar, A. & Cherner, M. (2020, February). *COMT Val158Met genotype alters the effects of methamphetamine dependence on dopamine and dopamine-related prefrontal cognition*. Paper presented at the 48th annual meeting International Neuropsychological Society, Denver, CO.
12. **Watson, C. W.-M.**, Kamalyan, L., Hussain, M. A., Tang, B., Collier, A. C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., McCutchan, J. A., Ellis, R., Grant, I., Heaton, R. K., & Marquine, M. J. for the CHARTER Group. (2019, November). *Ethnic/racial differences in longitudinal neurocognitive change among people living with HIV*. Poster presented at 39th annual meeting of the National Academy of Neuropsychology, San Diego, CA.

13. Paolillo, E. W., Saloner, R., Kohli, M., **Watson, C. W.-M.**, Heaton, R. K., & Moore, D. J. (2019, October). *Older age exacerbates negative effects of HIV and binge drinking on neurocognitive functioning*. Poster presented at the 10th International Workshop on HIV & Aging, New York City, NY.

14. Henry, B. K., 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*. Paper presented at the 3rd annual meeting of the Research Society on Marijuana, Vancouver, WA.

15. Paolillo, E. W., Saloner, R., Kohli, M., **Watson, C. W.-M.**, Heaton, R. K., & Moore, D. J. (2019, June). *Recent binge drinking relates to neurocognitive functioning in adults living with and without HIV*. Poster presented at the 42nd annual meeting of the Research Society on Alcoholism, Minneapolis, MN.

16. **Watson, C. W.-M.**, Pasipanodya, E., Ellorin, E. E., Corado, K. C., Flynn, R. P., Opalo, C., Lampley, E., Henry, B. L., Blumenthal, J. S., Bolan, R., Morris, S., & Moore, D. J. (2019, March). *Barriers and facilitators to PrEP initiation and adherence among transgender and gender non-binary individuals in Southern California*. Paper presented at the 2019 National HIV Prevention Conference, Atlanta, GA.

17. **Watson, C. W.-M.**, Sundermann, E. E., Morgan, E. E., Ellis, R. J., Letendre, S., Heaton, R. K, & Grant, I. (2019, February). *Cannabis exposure is associated with less neurocognitive impairment in people living with HIV*. Paper presented at the 47th annual meeting of the International Neuropsychological Society, New York City, NY.

18. Morgan E. E., Hussain, M. A., Iudicello J. E., **Watson, C. W.-M.**, Villalobos, J., Heaton, R. K., & Grant, I. for the TMARC Group. (2018, June). *Poor social cognition negatively influences methamphetamine addiction characteristics*. Poster presented at 16th annual meeting of the American Academy of Clinical Neuropsychology, San Diego, CA.

19. **Watson, C. W.-M.**, Montoya, J. L, Iudicello, J. E., Villalobos, J., Heaton, R. K., Grant, I., & Morgan E. E. for the TMARC Group. (2018, June). *Alexithymia and emotion dysregulation are associated with worse psychosocial outcomes in methamphetamine users*. Poster presented at 16th annual meeting of the American Academy of Clinical Neuropsychology, San Diego, CA.

20. Iudicello, J. E., Morgan, E. E., Hussain, M. A., Henry, S. M., **Watson, C. W.-M.**, Heaton, R. K., Grant, I. & the TMARC Group. (2018, June). *Emotional and psychosocial functioning are problematic in HIV and methamphetamine use and associated with significant functional and health-related outcomes*. Poster presented at 16th annual meeting of the American Academy of Clinical Neuropsychology, San Diego, CA.
21. Noble, J. M., Burkett, S., Cheng, B., Chen, Y., Shariff, J. Celenti, R., **Watson, C. W.-M.**, & Papapanou, P. N. (2018, June). *Cross-sectional associations between human oral microbiome next generation sequencing and cognitive impairment in a multi-ethnic elderly population*. Paper presented at the 7th annual meeting of the International Human Microbiome Consortium, Killarney, Ireland.

22. **Watson, C. W.-M.**, Iudicello J. E., Letendre, S., Morgan E. E., Kamat, R. Pérez-Santiago, J., Ellis, R. J., Heaton, R. K., & Grant, I. (2018, May). *Plasma soluble CD14 is associated with apathy in adults with a history of methamphetamine dependence*. Poster presented at the 73rd annual meeting of the Society of Biological Psychiatry, New York City, NY.

23. Alakkas, A., Ellis. R. J., **Watson, C. W.-M.**, Umlauf, A., Heaton, R. K., Letendre, S., Collier, A., Marra, C., Clifford, D. B., Gelman, B., Sacktor, N., Morgello, S., Simpson, D., McCutchan, J. A., Kallianpur, A., Gianella, S., Marcotte, T., Grant, I., & Fennema-Notestine, C. for the CHARTER Group. (2017, March). *Cerebral volumetric and metabolic abnormalities in HIV-associated neurocognitive disorders (HAND)*. Poster presented at the 142nd annual meeting of the American Neurological Association, San Diego, CA.

24. Moore, R. C., Hussain, M. A., **Watson, C. W.-M.**, Fazeli, P. L., Marquine, M. J., Yarns, B. C., Jeste, D. V., & Moore, D. J. (2017, October). *Grit as a protective factor for optimizing cognitive and everyday functioning among adults living with HIV*. Poster presented at the 8th International Workshop on HIV and Aging, New York City, NY.

25. **Watson, C. W.-M.**, Marquine, M. J., Moore, R. C., Heaton, A., Perez-Tejada, A., Umlauf, A., Morgan, E. E., Hussain, M. A., Cherner, M., Ellis, R., Grant, I., & Heaton, R. K. (2017, August). *Racial/ethnic differences in neurocognitive performance among people living with HIV*. Paper presented at the 125th annual meeting of the American Psychological Association, Washington D.C.

26. Hussain, M. A., Iudicello, J. E., Morgan, E. E., Villalobos, J., **Watson, C. W.-M.**, Minassian, A., Heaton, R. K., & Grant, I. and the TMARC Group. (2017, August). *Age-related differences on the Virtual Reality Functional Capacity Assessment Tool (VRFCAT) in HIV infected (HIV+) and/or methamphetamine dependent (METH+) adults*. Paper presented at the 125th annual meeting of the American Psychological Association, Washington D.C. *Recipient of the Division 40-Clinical Neuropsychology Blue Ribbon Award

27. **Watson, C. W.-M.**, Manly, J. J., Brickman, A. M. & Zahodne, L. B. (2017, February). *Racial discrimination is associated with cortical thinning in older African Americans*. Poster presented at the 45th annual meeting of the International Neuropsychological Society, New Orleans, LA.

28. Noble, J. M., **Watson, C. W.-M.**, & Papapanou, P. N. (2017, March). *Cross-sectional associations between clinical and serological evidence of periodontal disease and cognitive impairment in a multi-ethnic elderly population*. Poster presented at the 69th annual meeting of the American Academy of Neurology, Boston, MA.

29. **Watson, C. W.-M.**, Zahodne, L. B., Schupf, N., Tang, M., Brickman, A. M. & Manly, J. J. (2016, February). *Socioeconomic and educational factors account for racial inequities in dementia incidence in a community dwelling population*. Paper presented at the 44th annual meeting of the International Neuropsychological Society, Boston, MA.

30. Bertola, L., Zahodne, L. B., Angevaare, M., **Watson, C. W.-M.**, Schupf, N., & Manly, J. J. (2016, February). *Sociodemographic and cognitive predictors of memory trajectories across educational groups*. Paper presented at the 44th annual meeting of the International Neuropsychological Society, Boston, MA.

31. Noble, J. M., **Watson, C. W.-M.**, Burkett, S., & Papapanou, P. N. (2015, March). *Self-perceived versus actual oral health status among WHICAP participants*. Poster presented at the 93rd annual meeting of the International Association for Dental Research, Boston, MA.

32. Papapanou P. N., Burkett, S., **Watson, C. W.-M.**, & Noble, J. M. (2015, March). *Oral health status among elderly participants in the WHICAP study*. Poster presented at the 93rd annual meeting of the International Association for Dental Research, Boston, MA.

ABSTRACT OF THE DISSERTATION

Effects of Cannabis Exposure on Neuroinflammation, Neurocognition, and Everyday Function in HIV and Aging

by

Caitlin Wei-Ming Watson

Doctor of Philosophy in Clinical Psychology

University of California San Diego, 2022
San Diego State University, 2022

Professor Igor Grant, Chair

HIV and aging have adverse effects on the central nervous system (CNS), including chronic inflammation, and confer risk for neurocognitive impairment (NCI) and functional decline. Cannabis may exert beneficial effects on the CNS in people with HIV (PWH) due to its anti-inflammatory and immunomodulatory properties. Yet to date, there is scant literature examining the role of cannabis and cannabinoids in this population. This staple dissertation aimed to elucidate the relationships among cannabis exposure, central and peripheral inflammation, and neurocognitive and functional impairment in PWH.

Study 1 (*N* = 952; Watson et al., 2020). PWH with past-year cannabis use and past cannabis use disorder had lower rates of NCI (OR = 0.53, *p* = 0.009) and better performance in

learning (b = 2.70, p = 0.02) and verbal fluency (b = 2.86, p = 0.02) compared to non-cannabis-using PWH. Cannabis use was unrelated to NCI among people without HIV.

Study 2 (N = 234; Watson et al., 2021). Lower levels of pro-inflammatory biomarkers CCL2/MCP-1 and CLCX10/IP-10 in cerebrospinal fluid were observed among daily cannabis-using PWH with Δ^9-tetrahydrocannabinol (THC) positive urine toxicology compared to non-cannabis-using PWH (p = 0.02; p = 0.04). Plasma biomarkers showed no differences by cannabis use. Lower levels of CCL2/MCP-1 and CLCX10/IP-10 were associated with better learning (b = –6.3, p = 0.02; b = –2.3, p = 0.04).

Study 3 (N = 297; Watson et al., in preparation). In a longitudinal cohort of older adults with HIV, occasional cannabis use (≤ weekly) was associated with better overall global neurocognition (b = 0.50, p = 0.03), while THC+ urine toxicology showed negative short-term effects on memory (b = –0.27, p = 0.03). Rates of neurocognitive decline and functional declines did not differ by cannabis use.

Collectively, these studies extend pre-clinical cannabinoid findings identifying beneficial cannabis effects on neuroinflammation and neurocognition in the context of HIV and THC-specific short-term detrimental impacts in older adults. Results highlight the complex influence of cannabis on CNS function, which varies by dose/frequency, cannabinoid content, and pro-inflammatory disease context, and can inform future development of cannabinoid-based therapeutics to treat neuroinflammation and improve downstream outcomes in HIV and aging.

INTRODUCTION

Older age and HIV disease are each independently associated with central nervous system (CNS) injury, including increased inflammation and neural damage (Neuhaus et al., 2010; Xia et al., 2016), and consequently elevate risk for neurocognitive and functional impairment. For people with HIV (PWH), neurocognitive impairment remains prevalent in the era of life-extending antiretroviral therapy (ART). An estimated 25-50% of PWH show primarily mild to moderate neurocognitive impairment in the United States (U.S.), (Heaton et al., 2011b; Sacktor et al., 2016), with highest rates among PWH ages 50 and older (Valcour, 2013; Valcour et al., 2004a), who represent over half of the national HIV-positive (HIV+) population (Nakagawa, May, & Phillips, 2013). Increasing age is the greatest known risk factor for developing progressive, neurodegenerative dementias such as Alzheimer's Disease. In the U.S., the prevalence of dementia for people ages 65 and older is estimated to be 10% (Hebert, Weuve, Scherr, & Evans, 2013), with risk for dementia doubling every five years after the age of 65.

Together, aging with HIV appears to inflict additive, or possible synergistic, detrimental effects on the CNS, leading to substantially increased risk for impairment (Deeks, 2011; Valcour, Shikuma, Watters, & Sacktor, 2004b). Clinically, neurocognitive impairment among PWH is associated with deficits in everyday function including employment, medication adherence, and driving outcomes (Heaton et al., 2004; Vance, Fazeli, Ball, Slater, & Ross, 2014; Woods et al., 2009), and confers increased risk for early mortality (Vivithanaporn et al., 2010). Identifying factors that influence vulnerability to neurocognitive impairment among PWH and older adults is vital to maintaining optimal health in these vulnerable populations. Cannabis use represents one modifiable exposure of major current public health interest and is worthy of investigation as an agent of risk or resilience in neurocognitive and functional decline.

Cannabis Use and Therapeutic Potential in People with HIV and Older Adults

Cannabis use is highly prevalent among PWH in the U.S. with self-reported use in the past year nearly three times greater than that of the general population (Okafor et al., 2017; Pacek, Towe, Hobkirk, Nash, & Goodwin, 2018). Many PWH report use of cannabis to ameliorate symptoms of HIV/AIDS such as neuropathic pain, nausea, mood problems, and appetite and weight loss (Whiting et al., 2015; Woolridge et al., 2005). Randomized clinical trials of cannabis and cannabinoids show moderate evidence of clinical benefit for appetite stimulation/weight gain in HIV/AIDS and HIV-associated sensory neuropathy (Abrams et al., 2007; Beal et al., 1995; Ellis et al., 2009; Whiting et al., 2015).

Among older adults ages 50 and up, cannabis use has increased rapidly over the past 15 years in the context of expanding state-based legalization of medical and recreational cannabis, shifting cultural attitudes, and widespread marketing of cannabis products to treat a host of conditions (Lloyd & Striley, 2018). Reports from the National Survey on Drug Use and Health show that among older adults ages 50-64, past year cannabis use increased from 2.8% in 2006 to 9.0% in 2016, reflecting a 221% jump while among older adults ages 65 and up, past year cannabis use increased from 0.4% in 2006 to 2.9% in 2016, reflecting a 625% jump (Han et al., 2017); similar findings were observed in another national survey (Maxwell, Jesdale, & Lapane, 2021). Thus, while fewer older adults use cannabis compared to younger age groups, cannabis use among older adults is expanding faster than any other age group in the U.S.

Aging is associated with increased risk for chronic disease with 50% of adults ages 45–64 in the U.S. living with two or more chronic conditions and 81% among adults ages 65 and older (Buttorff, Ruder, & Bauman, 2017). Older adults endorse cannabis use at least in part for medical purposes, and estimates of medical use, including mixed medical and recreational use,

range from 21% (Choi, DiNitto, & Marti, 2017) to 82% (Sexton, Cuttler, & Mischley, 2019) to 93% (Yang et al., 2021) across varied contexts from the 2012-2013 National Epidemiologic Survey on Alcohol and Related Conditions, a 2013-2018 online survey from Washington State cannabis retail outlets and cannabis-related websites, and a 2019 geriatric clinic survey in San Diego, respectively. Older adults are increasingly turning to cannabis to address health conditions such as chronic pain, arthritis, sleep disturbances, anxiety, depression, migraines, and neuropsychiatric symptoms in late-life dementias and Parkinson's Disease (Hazekamp, Ware, Muller-Vahl, Abrams, & Grotenhermen, 2013). For some patients, conventional pharmaceutical products fail to adequately reduce symptoms or result in undesirable side effects, which may motivate interest and initiation of medical cannabis products. In the 2019 geriatric clinic survey, over 75% of medical cannabis users reported cannabis was "somewhat" or "extremely" helpful in managing their targeted health condition, and only 15% reported adverse side effects with dizziness and anxiety as most commonly reported.

Despite an increase in interest and use, robust evidence of cannabis' therapeutic effects on common health conditions, and specifically among aging populations is limited (Hillen, Soulsby, Alderman, & Caughey, 2019; National Academies of Sciences & Medicine, 2017). Data on efficacy and safety of medical cannabinoids established in mid-life adults cannot easily be generalized to older patient groups given age-related changes in drug metabolism and neurotransmitter sensitivity, which can alter drug efficacy and increase risk of adverse effects. A 2014 systematic review of medical cannabinoids use in older adults found some low-quality evidence of efficacy for treatment of anorexia and behavioral symptoms in dementia, and no efficacy for dyskinesia, breathlessness, and chemotherapy-induced nausea and vomiting (van den Elsen et al., 2014). Sedation and lethargy were the most common adverse effects reported, which

could be of clinical importance if these effects increase fall risk in older adults. In contrast, a potential favorable outcome of medical cannabis use may be its role in deprescribing efforts among older adults. Polypharmacy, typically defined as concurrent use of five or more prescription drugs, is common among older adults at an estimated 36% and linked to numerous safety concerns including major drug-drug interactions (Qato, Wilder, Schumm, Gillet, & Alexander, 2016). Opioid and benzodiazepine use in particular are concerning in aging populations due to their addictive potential and serious adverse effects with chronic use. A 2017 survey found that 41% of adults with past-year cannabis and opioid use reported a decrease or cessation of opioid use due to cannabis use (Ishida et al., 2019), and a 2013-2016 survey of current adult cannabis users found 46% reported using cannabis as a substitute for prescription drugs such as opioids, benzodiazepines, or anti-depressants (Corroon Jr, Mischley, & Sexton, 2017), but this work has not been replicated in aging populations. It is critical to expand age-specific knowledge regarding the benefits and risks of cannabis use as more older adults consider cannabis for recreational and medical use (Scott, Brennan, & Benitez, 2019).

Anti-Inflammatory and Neuroprotective Properties of Cannabis

Growing research investigates the therapeutic potential of cannabis and cannabinoids in aging, inflammatory, and autoimmune diseases (Klein, 2005; Nagarkatti, Pandey, Rieder, Hegde, & Nagarkatti, 2009; Whiting et al., 2015). The majority of current research on specific cannabinoids or phytocannabinoids, the active components of the cannabis plant, has centered on Δ^9-tetrahydrocannabinol (THC), and to an increasing extent non-intoxicating cannabidiol (CBD), while a limited number of studies examine effects of the other 120+ identified cannabinoids, including cannabigerol (CBG), cannabichromene (CBC), and cannabinol (CBN).

Evidence from pre-clinical and human studies show that cannabis can exert therapeutic and neuroprotective effects partially via manipulation of the endocannabinoid system. The most well-characterized components of the endocannabinoid system consist of cannabinoid type 1 (CB_1) and type 2 (CB_2) receptors and endogenous cannabinoids *N*-arachidonoylethanolamine or anandamide (AEA) and 2-arachidonoylglycerol (2-AG), while a complex enzyme and transporter apparatus synthesizes and catabolizes these compounds (Basavarajappa, Shivakumar, Joshi, & Subbanna, 2017; Kaur, R Ambwani, & Singh, 2016). CB_1 receptors are the most abundant G-protein-coupled receptors in the CNS and are densely concentrated in numerous brain region including the hippocampus, cerebellum, basal ganglia, hypothalamus, and amygdala, which underlie critical functions such as memory, coordinated motor function, appetite, and fear-related behaviors (Iversen, 2003). Manipulation of CB_1 receptors can regulate excitotoxic glutamatergic activity and may useful for multiple CNS disorders in which excessive stimulation of glutamate receptors and pathologically high levels of glutamate lead to neuronal injury and death (Zoppi et al., 2011). Meanwhile, CB_2 receptors are primarily expressed in the immune system and peripheral nerve tissues, and their expression increases under conditions of high inflammation (Onaivi, Ishiguro, Gu, & Liu, 2012). Targeting CB_2 receptors that mediate anti-inflammatory and immunomodulatory actions may be particularly important for pathogenic pro-inflammatory conditions (Chen, Gao, Gao, Su, & Wu, 2017; Rom & Persidsky, 2013).

Cannabinoid administration in mouse models demonstrates apoptosis of activated immune cells such as T cells and macrophages (Nagarkatti et al., 2009; Persidsky et al., 2015), downregulation of pro-inflammatory cytokine and chemokine production (Nagarkatti et al., 2009), and inhibition of synapse loss and neural injury (Kim, Shin, & Thayer, 2011). *In vitro*, THC treatment has been shown to suppress a number of pro-inflammatory factors including

TNF-α, IL-6, and IL-8, and decreased NF-κB secretion in human osteosarcoma cells (Yang, Li, Han, Jia, & Ding, 2015) as well as monocyte-derived interleukin IL-1ß production and astrocyte secretion of CCL2/MCP-1 and IL-6 from a human coculture system (Rizzo et al., 2019).

In aging populations, modulation of the endocannabinoid system in pre-clinical studies demonstrate its regulatory role in normal and pathological aging (Di Marzo, Stella, & Zimmer, 2015). In mouse models, global deletion of CB_1 receptors shows an accelerated aging phenotype with loss of hippocampal CA1 and CA3 neurons, increased microglia activation, and increased level of pro-inflammatory cytokines (Bilkei-Gorzo et al., 2012). Low dose THC administration appears to prevent neuroinflammation, induce neurogenesis, and improve cognitive performance in domains of learning, spatial memory, and cognitive flexibility in older male and female mice (Bilkei-Gorzo et al., 2017; Sarne, Toledano, Rachmany, Sasson, & Doron, 2018; Suliman, Taib, Moklas, & Basir, 2018). Further, cannabinoid-induced neuroprotective effects are observed on amyloid-beta and tau, key pathological markers of Alzheimer's Disease, including suppression of amyloid aggregation via competitive inhibition of acetylcholinesterase, and reduction of tau hyperphosphorylation (Aso, Juvés, Maldonado, & Ferrer, 2013; Aso, Sánchez-Pla, Vegas-Lozano, Maldonado, & Ferrer, 2015; Eubanks et al., 2006; Ramírez, Blázquez, del Pulgar, Guzmán, & de Ceballos, 2005).

HIV disease is associated with chronic immune activation, elevated circulating activated monocytes, and central and peripheral inflammation (Hong & Banks, 2015). Recent studies suggest that these pro-inflammatory processes, in particular chronic astrocyte production of cytokines and chemokines, contribute to CNS dysfunction, including HIV-associated neurocognitive impairment (Cohen et al., 2011; Imp et al., 2017; Saylor et al., 2016). Current cannabis use shows anti-inflammatory activity on activated and inflammatory monocyte

frequencies among PWH (Castro et al., 2019; Manuzak et al., 2018; Rizzo et al., 2018). While in plasma, biomarkers of microbial translocation, barrier integrity, and inflammation largely showed no differences by cannabis exposure; only MIP-1α and CXCL10/IP-10 showed lower expression in cannabis-using compared to non-cannabis-using PWH (Manuzak et al., 2018; Rizzo et al., 2018). In contrast, higher levels of plasma soluble cluster of differentiation 14 (sCD14) and plasma interleukin-1β have also been observed among cannabis-using compared to non-cannabis-using PWH (Castro et al., 2019; Krsak et al., 2020). Taken together, human studies in HIV show mixed inflammatory findings, while pre-clinical studies point to numerous mechanisms by which cannabinoids regulate pro-inflammatory and neurotoxic processes. No studies have yet reported no cannabis effects on inflammatory markers in cerebrospinal fluid (CSF) in HIV disease, which may be useful for characterizing CNS inflammation and linkage to neurocognitive and functional outcomes.

Cannabis Effects on Neurocognition (cross-sectional)

While cannabis use has been consistently linked with adverse effects on cognition, and in particular on memory, psychomotor, and executive function during acute intoxication (Broyd, van Hell, Beale, Yücel, & Solowij, 2016), the chronic effects of cannabis use on cognition are more methodologically challenging to determine (Gonzalez, 2007). Mouse model studies show acute THC administration induces dose and time-dependent signaling in cells expressing CB_1 and serotonin 5-HT2A receptors, and suggest the acute amnesic-like effects of cannabis use including cognitive impairment may be mediated by receptor heteromers, which regulate receptor activity (Puighermanal, Busquets-Garcia, Maldonado, & Ozaita, 2012; Viñals et al., 2015). Among recent studies examining chronic effects (i.e., “residual” effects observed in the absence of acute intoxication) of cannabis use on neurocognition in the general population,

cohorts results are highly inconsistent. Although large scale reviews indicate that the most consistent adverse effects of cannabis use are on verbal learning and memory (Broyd et al., 2016; Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003), chronic effects on all other neurocognitive domains (e.g., executive function, processing speed, working memory) vary widely by study, with many reporting no differences between cannabis users and non-users. A meta-analysis reported no residual negative effect of cannabis use on any neurocognitive domain after 25 days of abstinence (Schreiner & Dunn, 2012), suggesting that recovery of cognitive abilities with cessation of cannabis use and that previous studies' conclusions regarding the permanence of adverse cannabis effects may not have sufficiently adjusted for recency or use nor shared risk factors. Considerable variability in cannabis-associated neurocognitive outcomes may be explained by factors that differ within and across studies, such as dose and frequency of cannabis use, route of administration, type and potency of cannabis-based product (whole-plant, purified, or synthetic, cannabinoid composition), and context of use (e.g., age of use; social context and motivation for use, concurrent use with other substances, use in the presence of HIV disease or other pro-inflammatory conditions). These potential moderating factors are understudied, and their examination may identify critical conditional effects of cannabis use on neurocognitive function (Gonzalez, Pacheco-Colon, Duperrouzel, & Hawes, 2017).

For example, previous research has shown that in certain conditions known to have detrimental effects on cognition (e.g., heavy methamphetamine use; schizophrenia), cannabis use does not compound these detrimental effects, and may even be associated with reduced risk for neurocognitive impairment (Gonzalez et al., 2004; Yucel et al., 2012). In PWH, a small number of cross-sectional studies show adverse, null, and protective effects of cannabis on neurocognitive function. Adverse findings were detected most frequently on cognitive domains

of learning and memory/delayed recall, and selectively among heavier cannabis users (Thames, Mahmood, Burggren, Karimian, & Kuhn, 2016), among early onset users (Skalski, Towe, Sikkema, & Meade, 2018), and in more severe HIV disease (Cristiani, Pukay-Martin, & Bornstein, 2004). Null cannabis effects on neurocognitive performance across all domains are also observed (Chang, Cloak, Yakupov, & Ernst, 2006; Chang, Wang, Liang, Ernst, & Oishi, 2020). In in one study, light cannabis using PWH (at least weekly use, less than 2 times per day) showed higher verbal fluency compared to HIV-negative light cannabis users (Thames et al., 2016). Two recent studies found measures of past cannabis use were associated with better neurocognitive performance in domains of executive function and psychomotor speed (Kallianpur et al., 2020) and processing speed, visual learning and memory, and motor skills (Crook et al., 2020). Thus, the current literature investigating the neurocognitive effects of cannabis use in the context of HIV disease is highly mixed, indicating that any beneficial or harmful effects on cognition are likely contingent on moderating cannabis-level or individual-level factors.

Among older adults, a 2019 systematic review of 26 studies examined effects of cannabis on cognitive functioning in adults ages 50 and older with and without neurocognitive disorders (Scott et al., 2019). In sum, worse neurocognitive performance, primarily in verbal memory, was detected in some studies with higher doses and heavier history of lifetime use of cannabis (Auer et al., 2016; McKetin, Parasu, Cherbuin, Eramudugolla, & Anstey, 2016), while the majority of studies found no cognitive differences between cannabis users and non-users (Burggren et al., 2018; Thayer, YorkWilliams, Hutchison, & Bryan, 2019) and others found modest improvements in primarily subjective cognition among cannabis users (Sexton et al., 2019). Use of cannabis for medical purposes was associated with better cognitive outcomes; medical users

may use products with less THC and experience symptom relief that contributes to better cognitive function (Colizzi & Bhattacharyya, 2017). Some older adults may be more vulnerable to adverse effects of cannabis due to decline in cognitive abilities with normal aging and age-related changes in pharmacokinetic factors such as slowed metabolism.

To our knowledge, there are only two studies with small sample sizes that examine effects of cannabis use on brain structure and cognitive performance among older adults (Burggren et al., 2018; Thayer et al., 2019). In Thayer et al. (2019), current cannabis (at least weekly users) (n = 28) and non-cannabis users (n = 28) ages 60 and older showed no differences in total gray matter, total white matter, nor global CSF volume after controlling for age and depression symptoms. Cannabis users showed greater left putamen, left lingual cortex, and rostral middle frontal cortex regional volumes. Performance in seven cognitive domains showed no differences by cannabis use, but cognitive performance analyses were underpowered (Thayer et al., 2019). In Burggren et al. (2018), older adults with a history of heavy cannabis use in adolescence (at least 20 days/month for at least one year before age 20, with on average 29 years of abstinence) (n = 24) exhibited thinner hippocampal cortex compared to non-users (n = 26) controlling for age, sex/gender, reading level, years of education, and cigarette use. No significant differences in cognitive performance were observed. Overall, the evidence base in older adults shows mixed results, lack of high-quality studies, and is highly heterogenous in terms of cohort characteristics, study design, cannabis product and level of use, and cognitive outcome measures, precluding any meta-analysis (Scott et al., 2019). In order to clarify the potential neuroprotective benefits or risks of cognitive decline in this vulnerable population, there is a need for research with larger sample sizes, standardized assessment of cannabis use, and longitudinal neurocognitive data.

Cannabis Effects on Neurocognition (longitudinal)

Longitudinal studies examining the influence of cannabis use on cognitive trajectories over time in the general population show some evidence of cognitive declines in a recent review (Gonzalez et al., 2017). Memory (immediate and delayed recall) and processing speed performance were the cognitive domains most likely to show worse trajectory in the heaviest cannabis using group. The magnitude of negative effects were often small, restricted to the heaviest cannabis users (daily), and were often attenuated considerably (at times to the point of non-significance) after controlling for relevant predictors of cognition such as sex/gender and years of education (Gonzalez et al., 2017; Tait, Mackinnon, & Christensen, 2011). Consistent with cross-sectional evidence, longitudinal studies show that after short periods of abstinence (three months), deficits associated with heavy cannabis use are recovered (Fried, Watkinson, & Gray, 2005; Tait et al., 2011).

Methodologically, longitudinal studies are crucial to disentangling cross-sectionally observed associations between cannabis use and cognitive outcomes. They can aid in making causal inferences regarding cannabis use and cognitive decline when they assess how changes in cannabis use prospectively influence cognitive trajectories or compare cognitive performance before and after cannabis use onset. In longitudinal cohorts, assessment and control of predisposing factors that may contribute to both heavy, chronic cannabis use and worse neuropsychological outcomes as shared risk factors is crucial (Rogeberg, 2013). The majority of longitudinal studies in this area have been conducted among young adults (Koenders et al., 2017), and among generally healthy individuals. Thus, conclusions drawn from these studies may not generalize to other populations vulnerable to cognitive decline, such as older adults and people living with chronic diseases such as HIV.

Independence in Everyday Function and Cannabis Use

HIV- and age-associated cognitive declines are linked to worse functioning in activities of daily living (ADLs), including financial and medication management (Heaton et al., 2004; Tucker-Drob, 2011; Vance, Wadley, Crowe, Raper, & Ball, 2011). For PWH and older adults, independence in ADLs is crucial to maintaining quality of life. Longitudinal research in older adults indicates decline in both neurocognitive performance and everyday function in normal aging (Tucker-Drob, 2011). Among PWH, memory impairment and intra-individual neurocognitive variability both confer risk of ADL dependence above and beyond age, HIV disease, psychiatric, and substance use predictors (Morgan, Woods, & Grant, 2012b; Woods et al., 2008). Evidence for synergistic detrimental effects of aging and HIV disease on self-report and performance-based measures of everyday function have been observed (Morgan et al., 2012a).

In the general population, one longitudinal study of heavy cannabis use and neurocognitive function from childhood to midlife in the general population examined everyday function by asking third-party informants whether cannabis-induced neurocognitive impairment translated into functional problems in daily life (Meier et al., 2012). Informants were asked whether participants had problems with their attention or memory at age 38 that influenced ability to perform ADLs. Informants reported more disruptive memory and attentional problems in adults with persistent cannabis dependence, controlling for childhood IQ. Thus, heaviest users meeting criteria for a cannabis substance use disorder over multiple waves of study follow-up showed impairment in daily functioning as observed by close informants. To our knowledge, there are no studies that explicitly examine influence of current cannabis use on neurocognition and ability to perform ADLs among PWH or older adults in cross-sectional nor longitudinal

study designs. Inclusion of measures of everyday function in studies of neurocognition allow researchers to investigate whether cannabis effects observed on neurocognitive performance extend to ability to independently perform ADLs, enhancing the ecological validity and real-world relevance of neurocognitive findings.

Specific Aims and Hypotheses

PWH and older adults are at elevated risk for chronic inflammation as well as neurocognitive and functional decline. There is a lack of treatments to address neuroinflammation in HIV disease and late-life neurodegenerative diseases. This dissertation aimed to evaluate the role of cannabis use on central and peripheral inflammation, neurocognitive performance, and functional outcomes in populations at risk for impairment. Based on the pre-clinical literature demonstrating anti-inflammatory and neuroprotective properties of cannabis, we hypothesized broadly that in the context of pro-inflammatory processes in HIV and aging, cannabis exposure would relate to lower central and peripheral inflammation and better neurocognitive and functional outcomes in these populations. We further hypothesized that some moderate levels of cannabis use are protective for neurocognitive outcomes among PWH, while heavy, high-dose cannabis use would likely disrupt endocannabinoid system homeostasis, resulting in poor neurocognitive outcomes (Figure 1).

Study 1. Examined effects of cannabis use, aging, and HIV on global neurocognitive impairment and cognitive domain performance. In this cross-sectional study of 952 adults (PWH n = 679; HIV-negative people n = 273), we examined the independent and interactive effects of aging, HIV status, and cannabis use on neurocognitive impairment and performance in seven cognitive domains. **Hypothesis 1a.** We hypothesized we would detect a 3-way age X HIV X cannabis interaction such that cannabis exposure would relate to less neurocognitive

impairment among younger and older PWH, but the magnitude of the association would be greater among older PWH. We hypothesized cannabis exposure would be unrelated to rates of neurocognitive impairment among HIV-negative individuals. **Hypothesis 1b.** Among PWH, cannabis use would relate to better performance in cognitive domains such as verbal fluency.

Study 2. Examined the relationship between cannabis use and central and peripheral inflammatory biomarkers in HIV disease, and cognitive relevance of these biomarkers. In this cross-sectional study of 234 adults, levels of six inflammatory biomarkers in CSF and plasma (IL-6, CCL2/MCP-1, CLCX-10/IP-10, sCD14, sTNFR-II, TNF-α) were compared across four groups categorized by HIV status and cannabis use: HIV-negative non-cannabis users (n = 65), HIV+ non-cannabis users (n = 105), HIV+ moderate cannabis users (average weekly use) (n = 62), and HIV+ daily cannabis users (n = 31). To determine functional relevance of any inflammatory findings, relationships between inflammatory biomarkers and performance in seven cognitive domain were also assessed. **Hypothesis 2a.** We hypothesized that moderate cannabis-using or daily-cannabis using PWH would show lower levels of some pro-inflammatory biomarkers such as CLCX10/IP-10 and TNF-α compared to non-cannabis-using PWH. **Hypothesis 2b.** We hypothesized that lower levels of biomarkers associated with cannabis use would be predict better performance in cognitive domains identified by Study 1.

Study 3. Examined longitudinal associations between cannabis use and cognitive and everyday function among older adults with HIV. 297 older adults with HIV were followed longitudinally for up to 10 years with comprehensive assessments every 6–12 months (average years of follow-up = 3.9). Participants were classified based on patterns of average cannabis use across study follow-up as frequent cannabis users (>weekly) (n = 23), occasional cannabis users (≤weekly) (n = 83), and non-cannabis users (n =191). Measures of recent

cannabis use examined to capture short-term effects on cognition included: reported days of cannabis use in the past month, estimated grams of cannabis used in the past month, and THC+ urine toxicology at study visit. Multi-level models examined the effects of average and recent cannabis use on global cognition, global cognitive decline, and everyday function. Analyses by cognitive domain were also conducted. **Hypothesis 3a.** We hypothesized that average occasional cannabis use over study follow-up compared to no cannabis use would relate to higher overall global cognitive performance over study follow-up **Hypothesis 3b.** and less steep rates of global cognitive decline. **Hypothesis 3c.** We hypothesized that some measures of recent, heavier cannabis use would be associated with short-term decrements in cognitive performance.

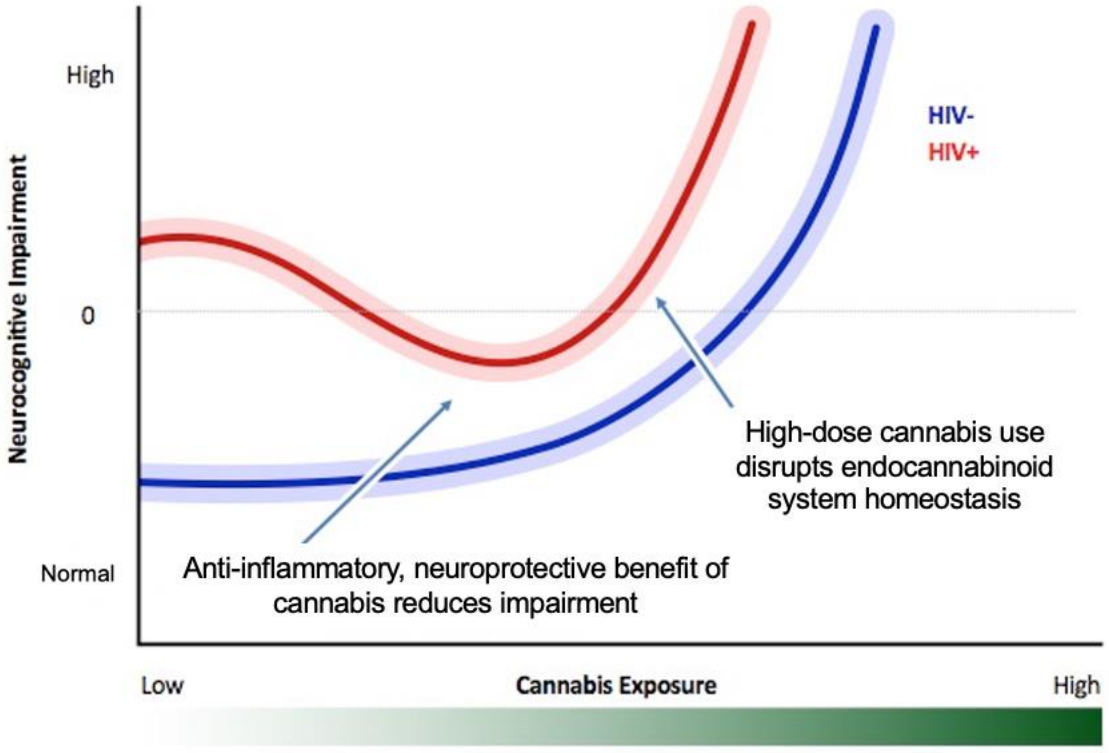

Figure 1. Theoretical model of beneficial vs. harmful effects of cannabis on neurocognitive impairment based on level of cannabis exposure and presence of HIV disease

CHAPTER 1

Cannabis Exposure is Associated with a Lower Likelihood of Neurocognitive Impairment in People Living with HIV

C. Wei-Ming Watson[1,2], Emily W. Paolillo[1,2], Erin E. Morgan[1], Anya Umlauf[1], Erin E. Sundermann[1], Ronald J. Ellis[1,3], Scott L. Letendre[4], Thomas D. Marcotte[1], Robert K. Heaton[1], & Igor Grant[1]

[1]Department of Psychiatry, University of California, San Diego; [2]San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology; [3]Department of Neurosciences, University of California, San Diego; [4]Department of Medicine, University of California San Diego

ABSTRACT

Objective: Aging and HIV have adverse effects on the central nervous system, including increased inflammation and neural injury and confer risk of neurocognitive impairment (NCI). Previous research suggests the nonacute neurocognitive effects of cannabis in the general population are adverse or null. However, in the context of aging and HIV, cannabis use may exert beneficial effects due to its anti-inflammatory properties. In the current study, we examined the independent and interactive effects of HIV and cannabis on NCI and the potential moderation of these effects by age.

Methods: Participants included 679 people living with HIV (PLHIV) and 273 people living without HIV (HIV–) (18–79 years old) who completed neurocognitive, neuromedical, and substance use assessments. NCI was defined as a demographically corrected global deficit score $ 0.5. Logistic regression models examined the effects of age, HIV, cannabis (history of cannabis substance use disorder and cannabis use in past year), and their 2-way and 3-way interactions on NCI.

Results: In logistic regression models, only a significant interaction of HIV X cannabis was detected (P = 0.02). Among PLHIV, cannabis was associated with a lower proportion of NCI (odds ratio = 0.53, 95% confidence interval = 0.33–0.85) but not among HIV– individuals (P = 0.40). These effects did not vary by age.

Conclusions: Findings suggest cannabis exposure is linked to a lower odds of NCI in the context of HIV. A possible mechanism of this result is the anti-inflammatory effect of cannabis, which may be particularly important for PLHIV. Further investigations are needed to refine the effects of dose, timing, and cannabis compound on this relationship, which could inform guidelines for cannabis use among populations vulnerable to cognitive decline.

Cannabis Exposure is Associated With a Lower Likelihood of Neurocognitive Impairment in People Living With HIV

Caitlin Wei-Ming Watson, MS,[a,b] Emily W. Paolillo, MS,[a,b] Erin E. Morgan, PhD,[a] Anya Umlauf, MS,[a] Erin E. Sundermann, PhD,[a] Ronald J. Ellis, MD, PhD,[a,c] Scott Letendre, MD,[d] Thomas D. Marcotte, PhD,[a] Robert K. Heaton, PhD,[a] and Igor Grant, MD[a]

Background: Aging and HIV have adverse effects on the central nervous system, including increased inflammation and neural injury and confer risk of neurocognitive impairment (NCI). Previous research suggests the nonacute neurocognitive effects of cannabis in the general population are adverse or null. However, in the context of aging and HIV, cannabis use may exert beneficial effects due to its anti-inflammatory properties. In the current study, we examined the independent and interactive effects of HIV and cannabis on NCI and the potential moderation of these effects by age.

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Key Words: cannabis, marijuana, HIV/AIDS, NeuroAIDS, cognition, HIV associated neurocognitive disorders

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INTRODUCTION

The advent of combination antiretroviral therapy (cART) has allowed people living with HIV (PLHIV) who have stable access to HIV treatment to achieve life expectancies near those without HIV.[1] Despite medical advancements, neurocognitive impairment (NCI) remains prevalent, affecting 25%–50% of PLHIV,[2,3] with highest rates among older PLHIV.[4,5] Older age and HIV infection are each independently associated with central nervous system (CNS) injury, including increased inflammation and subsequent neural damage.[6,7] Together, aging with HIV seems to inflict additive, or possible synergistic, detrimental effects on the CNS, leading to substantially increased risk of NCI.[8,9] Clinically, NCI among PLHIV is associated with impairments in everyday functioning (eg, medication management)[10,11] that can impact progression of HIV, subsequent transmissibility, and even confer increased risk of early mortality. Thus, understanding factors that may increase risk of or resilience against NCI among PLHIV is vital to maintaining optimal health in this population.

Cannabis use/exposure represents one modifiable behavioral factor worthy of investigation as an agent of NCI risk or resilience. Cannabis use is highly prevalent among PLHIV, with self-reported use in the past year almost three times greater than that of the general population in the United States (U.S.).[12] Many PLHIV report the use of cannabis to ameliorate symptoms of HIV/AIDS such as neuropathic pain, nausea, mood problems, and appetite and weight loss.[13,14] Among older adults, medicinal cannabis use

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From the [a]Department of Psychiatry, University of California, San Diego, CA; [b]San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology; [c]Department of Neurosciences, University of California, San Diego, CA; and [d]Department of Medicine, University of California San Diego, San Diego, CA.

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Correspondence to: Caitlin Wei-Ming Watson, MS, HIV Neurobehavioral Research Program, 220 Dickinson Street, Suite B (8231), San Diego, CA 92103 (e-mail: c4watson@ucsd.edu).

has also increased as state-based legalization of medical and recreational cannabis has expanded in the U.S.[15,16] Among the numerous recent studies examining chronic effects (ie, "residual" effects observed in the absence of acute intoxication) of cannabis use on neurocognition in the general population, results are highly variable. Although large scale reviews indicate that the most consistent adverse effect of cannabis use is on verbal learning and memory;[17,18] chronic effects on all other neurocognitive domains (eg, executive function) vary widely by study, with many reporting no differences between cannabis users and non-users. A meta-analysis reported no residual negative effect of cannabis use on any neurocognitive domain after 25 days of abstinence,[19] suggesting that some previous conclusions about permanence of adverse cannabis effects on cognition might not have sufficiently adjusted for recency of use. Some variations in neurocognitive outcomes may be potentially explained by relevant factors that differ within and across studies, such as amount of cannabis use, type and potency of cannabis product, and the context of use (eg, age of use; concurrently with other substances; in the presence of HIV disease or other medical conditions). These potential moderating factors are understudied, and their examination may support possible conditional effects of cannabis use on neurocognitive function.[20]

For example, previous research has shown that in certain conditions known to have detrimental effects on cognition (eg, methamphetamine use; schizophrenia), cannabis exposure does not compound these detrimental effects and may even be associated with reduced risk of NCI.[21,22] Although there is some evidence that cannabis exposure may reduce neural injury by decreasing excitotoxicity and neuroinflammation,[23,24] studies examining this in the context of HIV disease and the downstream neurocognitive effects of cannabis use are sparse and inconsistent, with reported effects ranging from adverse to protective.[25–27] Furthermore, we are unaware of any studies examining chronic effects of cannabis on neurocognition in the context of HIV and aging. Given the current literature, one plausible hypothesis is that in the context of aging and HIV (two processes in which inflammation plays a role), cannabis exposure will relate to better cognitive outcomes compared to younger PLHIV and HIV− older adults without cannabis exposure.

The current study examined the combined impact of cannabis, HIV, and aging on cognition. The first aim was to examine rates of NCI across 4 groups categorized by HIV status and cannabis exposure (CAN+; CAN−). We hypothesized (1) among HIV− groups, NCI rates will not differ between cannabis groups, whereas (2) among PLHIV groups, the CAN+ group will have lower rates of NCI compared with the CAN− group. In our second aim, we examined whether the effects of HIV or cannabis exposure on NCI were moderated by age in a model controlling for relevant predictors of NCI. We hypothesized we would detect a 3-way age X HIV X cannabis interaction such that cannabis exposure would relate to less NCI among younger and older PLHIV, but the magnitude of the association would be greater among older PLHIV, and cannabis exposure would be unrelated to NCI among younger and older HIV− individuals. In our third study aim, we examined the effects of cannabis exposure by cognitive domain among any groups showing differential relationships between cannabis exposure and NCI in study aim 2.

METHODS

Participants and Design

Participants included 952 community-dwelling adults (PLHIV n = 679; HIV− n = 273) enrolled in various NIH-funded research protocols at the University of California San Diego's HIV Neurobehavioral Research Program (HNRP, https://hnrp.hivresearch.ucsd.edu/) including the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, HIV Neurobehavioral Research Center (HNRC) study, and NeuroAIDS study. Study details have been published elsewhere.[28–30] Study visits took place between 1998 and 2016 with 70.8% of visits after 2005. Exclusion criteria for the parent studies included history of non–HIV-related neurological, medical, or psychiatric disorders that affect brain function (eg, schizophrenia, traumatic brain injury, or epilepsy), learning disabilities, or a dementia diagnosis. Exclusion criteria for the current analyses also included (1) any non-cannabis substance use disorder in the past year (2) positive urine toxicology for illicit drugs (except cannabis) or a positive breathalyzer test for alcohol during study visits. Given the high rates of major depressive disorder (MDD) among PLHIV, estimated to range from 5% to 20%,[31,32] the current study had no exclusions for current or past MDD to increase generalizability of findings. The UCSD's Human Research Protections Program approved all study procedures, and all participants provided written informed consent.

Demographic Evaluation

Demographic information (age, years of education, sex/gender, race, and ethnicity) was obtained via self-report. Race and ethnicity were ascertained following NIH guidelines and consistent with the U.S. Census Bureau methodology.[33]

Substance Use and Psychiatric Evaluation

To evaluate current and past histories of substance use disorders (alcohol, cannabis, cocaine, methamphetamine, opioid, sedative, or hallucinogen) and MDD, the Composite International Diagnostic Interview (CIDI, v2.1) was administered. The CIDI is a computer-assisted, fully structured interview that provides an assessment of alcohol, drug, and mental disorders using DSM–IV criteria.[34] Study methodology was developed before the release of the DSM–5, and thus, DSM–IV criteria are used in assessment to maintain consistency of diagnoses across multiple longitudinal cohorts in our large research center. In accordance with DSM–IV criteria, substance abuse was met when participants endorsed substance use despite recurring problems (eg, interpersonal, work-related, physically hazardous, or legal) that result from substance use, and substance dependence was met when participants endorsed experiencing

symptoms of tolerance, withdrawal, and inability to control or cut-down substance use.[35] For each substance, abuse and dependence criteria were combined into one substance use disorder variable, consistent with previous studies that attempt to capture more than one definition of substance misuse[36] and to be more consistent with current DSM–5 criteria and terminology. Lifetime total days and quantity of cannabis use were also assessed through a modified timeline follow-back (TLFB) interview.[37] This modified TLFB assesses average quantities and frequencies of use during participant-identified periods in their life (eg, from age 20 to 23 years and age 23 to 28 years), starting from age of first use. These estimates are totaled to obtain an estimate of total lifetime days of use and total lifetime quantity of use. Although these are rough estimates, previous studies from our group have found distinct differences between estimates obtained from individuals who meet criteria for substance use disorders and those who do not.[38,39]

Cannabis exposure (CAN+) was defined as individuals with both a history of cannabis use disorder and cannabis use in the past year, to capture individuals with both substantial past use and recent exposure. Those in the no-cannabis exposure group (CAN−) had no history of cannabis use disorder and no cannabis use in the past year. Thus, individuals in this group may have had past cannabis exposure, but it was remote and not severe. Furthermore, any individuals in the CAN− group whose lifetime average grams per day of cannabis use exceeded 1 gram were excluded.

Neuromedical Evaluation

All participants underwent a comprehensive neuromedical assessment. Detailed medical and antiretroviral (ARV) usage history was captured via a structured, clinician-administered questionnaire. HIV infection was diagnosed by an enzyme-linked immunosorbent assay with Western blot confirmation. Duration of HIV disease was determined by date since the first positive HIV test. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, and $CD4^+$ T cells (flow cytometry) were performed. Levels of HIV viral load in plasma and CSF were measured using reverse-transcriptase polymerase chain reaction (Amplicor; Roche Diagnostics, Indianapolis, IN), with a lower limit of quantitation of 50 copies/mL. HIV viral load was dichotomized as detectable vs. undetectable at the lower limit of quantitation of 50 copies/mL.

Neuropsychological Evaluation

All participants completed neurocognitive tests of verbal fluency, executive function, processing speed, learning, delayed recall, working memory/attention, and motor skills. Specific tests that comprise each domain are displayed in Table 1. Raw test scores were transformed into normally distributed T-scores (M = 50; SD = 10), which are demographically adjusted for age, education, sex/gender, and race/ethnicity based on published normative samples of HIV− participants.[40,41] Cognitive domain summary T-scores were generated by averaging T-scores across tests within a cognitive domain. T-scores for each test were also converted into deficit scores that ranged from 0 (T>40; no impairment) to 5 (T<20; severe impairment). Deficit scores are averaged across all tests to obtain a Global Deficit Score.[42,43] The Global Deficit Score is therefore weighted to characterize severity of impairment and is not influenced by any exceptionally high test scores (study sample range: 0–3.8). Consistent with previous studies, NCI was dichotomized using a validated cut-point of GDS ≥0.5,[43,44] a score that represents performance that is at least mildly impaired on at least half of the tests.

Statistical Analyses

Participants were categorized into 4 groups based on HIV status and cannabis exposure (HIV−/CAN−, HIV−/CAN+, PLHIV/CAN−, and PLHIV/CAN+). Assumptions for parametric methods were checked. Group differences on demographic, psychiatric, substance use, and disease characteristics were examined using analysis of variance or Wilcoxon tests for continuous variables and χ^2 or Fisher exact tests for categorical variables. Pairwise comparisons were examined using Tukey HSD for continuous outcomes and Bonferroni-adjustments for dichotomous outcomes. Differences in cannabis exposure (CAN+ vs. CAN−) by HIV status and various demographic groupings (eg, age, sex/gender, race/ethnicity, and sexual orientation) were also examined using χ^2 statistics.

TABLE 1. Neurocognitive Battery: Individual Tests Comprising Each Neurocognitive Domain

Neurocognitive Domain	Individual Measures
Verbal fluency	Controlled oral word association test
	Category fluency (animals)
	Category fluency (actions)
Executive function	Wisconsin card sorting test (64-item)
	Trail making test, part B
	Stroop color word trial
Processing speed	WAIS-III digit symbol
	WAIS-III symbol search
	Trail making test, part A
	Stroop color trial
Learning	Learning trials of:
	Hopkins verbal learning test-revised
	Brief visuospatial memory test-revised
Delayed recall	Delayed recall trials of:
	Hopkins verbal learning test-revised
	Brief visuospatial memory test-revised
Working memory	WAIS-III letter-number sequencing
	PASAT (1st channel only)
Motor skills	Grooved pegboard test (dominant & nondominant hands)

PASAT, paced auditory serial addition task; WAIS III, Wechsler Adult Intelligence Scale, third edition.

Any variables that both differed between the 4 HIV/CAN groups at $P < 0.05$ and related to NCI at $P < 0.05$ were included as covariates when examining the relationships between age, HIV, and cannabis exposure on NCI. Criteria for covariates led to the inclusion of race/ethnicity, current MDD, and past methamphetamine use disorder in our models. None of the HIV disease characteristics differed by cannabis exposure and thus were not included as covariates.

For the first study aim, we examined rates of NCI across the four HIV/CAN groups with χ^2 tests unadjusted for covariates. For the second study aim, we used a data-driven approach to examine a potential 3-way interaction in a multivariate logistic regression model. Modeling our dichotomous NCI outcome as a function of age, HIV, cannabis exposure, and relevant covariates, we initially included a full-factorial 3-way interaction between age X HIV X cannabis and all lower-order 2-way interactions (age X HIV, age X cannabis, and HIV X cannabis). We then systematically removed any nonsignificant interactions from our model for a final analytic model. Age was treated as a continuous variable. For the third study aim, we examined the effect of cannabis exposure on 7 cognitive domain T-scores in separate multivariable linear regression models among groups showing differential cannabis–NCI relationships in study aim 2, and including relevant covariates. *P* values for the association of cannabis exposure with each cognitive domain were adjusted using the false discovery rate method for multiple comparisons.

Furthermore, given that a large portion of the PLHIV cohort (48.0%) was not virally suppressed, we conducted a subanalysis including only PLHIV with undetectable plasma HIV RNA (n = 345). Finally, given that the CAN− group showed a broader age range distribution (ages 18–79) compared with the CAN+ group (ages 18–65), we conducted a subanalysis excluding individuals aged 65 years and older, resulting in a restricted sample (n = 923). All covariates from whole sample models were included in the subanalysis models.

RESULTS

Study Cohort

Participants ranged in age from 18 to 79 years old (M = 43.2, SD = 11.7) and were predominantly men 76.4%. The majority of men identified as gay or bisexual (70.7%), whereas the majority of women identified as heterosexual (93.8%). In terms of race/ethnicity, the cohort was 49.8% White, 26.7% Black or African American, 17.3% Hispanic or Latino, and 6.2% other. Sample characteristics including demographic, psychiatric, substance use, and HIV disease and treatment variables by the HIV/CAN group are presented in Table 2.

Cannabis Characteristics

15.8% (n = 150) of the study sample fell into our CAN+ group. In terms of CAN+ older adults, there were 13 CAN+ PLHIV and 22 CAN+ HIV− individuals greater than 50 years old and no CAN+ individuals in either HIV status group who were greater than 65 years old. Cannabis use characteristics within the CAN+ group are presented in Table 3. The average age at the first use was 15.6 years old (SD = 5.0), average lifetime grams per day was 1.3 (SD = 1.8) [median = 0.6, interquartile range (IQR) = 0.3–1.5], and median days since the last use was 5 (IQR = 1–60.9). For the CAN+ group, the median total lifetime estimated grams of use was 1724 grams (IQR = 454–5542), and total lifetime estimated days of use was 2670 (IQR = 1105–5297). For the CAN− group, only 349 participants reported cannabis use (the remaining n = 453 reported no use or less than 5 uses in their lifetime), and in this subgroup, the median total lifetime estimated grams of use was 7.5 g (IQR = 1, 93), and total lifetime estimated days of use was 53 (IQR = 6, 470). For CAN− individuals with previous cannabis exposure, their cannabis use was highly remote, with an average of 13.9 years since the last use.

Cannabis exposure tended to be higher in younger adults (<age 50) compared with older adults (≥age 50), but this was not statistically significant ($P = 0.08$). Cannabis exposure did not differ by HIV status groups ($P = 0.85$) but was higher in men compared to women ($P < 0.001$) and in Whites and African Americans compared to Latinos ($P < 0.002$, $P < 0.02$, respectively). In terms of sexual orientation, bisexual individuals (n = 81, 91.7% men) had higher cannabis exposure compared to heterosexual and gay individuals, but this difference was not statistically significant ($P = 0.06$).

NCI Across HIV and Cannabis Groups

Rates of NCI differed significantly across HIV/CAN groups ($\chi^2 = 44.1$, df = 3, $P < 0.001$) (Fig. 1). In analyses unadjusted for covariates, among PLHIV (n = 679), NCI rates were lower for those with cannabis exposure ($\chi^2 = 14.3$, df = 1, $P < 0.001$). Conversely, among HIV− individuals (n = 273), NCI did not differ by cannabis exposure ($\chi^2 = 0.04$, df = 1, $P = 0.84$). In analyses with the PLHIV sample restricted to those with undetectable plasma HIV RNA viral load (n = 345), findings did not differ from the whole sample analyses.

Cannabis, HIV, and Age on NCI

Table 4 presents our multivariable logistic regression analysis findings predicting NCI. Controlling for race/ethnicity, current MDD, and past methamphetamine use disorder, the 3-way age X HIV X cannabis interaction was not significant ($P = 0.17$) (Table 4, model 1a), and thus, we removed it from our model. With only the lower-order 2-way interactions included, a significant cannabis X HIV interaction was detected ($P = 0.045$), whereas the age X cannabis interaction ($P = 0.10$) and the age X HIV interaction ($P = 0.93$) were not significant (Table 4, model 1b). When we removed the nonsignificant age interactions from our model, the cannabis X HIV interaction remained significant ($P = 0.02$) (Table 4, model 1c). Probing the cannabis X HIV interaction revealed that cannabis exposure was associated with lower odds of NCI among PLHIV [odds ratio (OR) = 0.53, 95% confidence interval (CI) = 0.33–0.85, $P = 0.009$] and was not related to NCI among HIV− individuals

TABLE 2. Cohort Characteristics (N = 952), Mean (SD), Median (IQR), or %

	HIV−/CAN− [1], n = 229	HIV−/CAN+ [2], n = 44	PLHIV/CAN− [3], n = 573	PLHIV/CAN+ [4], n = 106	Group diff. (*P*)	Group differences Pairwise comparisons	Association with NCI (*P*)
Demographics							
Age	43.4 (14.7)	37.8 (13.3)	43.7 (10.6)	42.4 (8.9)	0.01	[1], [3] > [2]	<0.001
Years of education	13.8 (2.4)	13.1 (2.6)	13.4 (2.8)	13.0 (2.3)	0.03	[1] > [4]	0.10
Sex/gender (% Women)	39.7%	20.5%	20.4%	7.5%	<0.001	[1] > [2], [3] > [4]	0.32
Ethnicity/race					<0.001	[3] > [1]*	0.05
White	57.2%	61.4%	44.9%	55.7%			
Black/African American	16.2%	22.7%	30.5%	30.2%			
Latino/Hispanic	17.0%	6.8%	19.6%	10.4%			
Other	9.6%	9.1%	5.1%	3.8%			
Sexual orientation (% gay or bisexual)	22.5%	27.3%	67.0%	75.5%	<0.001	[3], [4] > [1], [2]	0.38
Psychiatric							
Current MDD	3.5%	6.8%	13.1%	14.2%	<0.001	[3], [4] > [1]	0.005
Lifetime MDD	25.3%	29.6%	43.6%	58.5%	<0.001	[4] > [3] > [1], [2]	0.34
Substance use							
Past alcohol use disorder	21.8%	68.2%	32.6%	67.9%	<0.001	[2], [4] > [3] > [1]	0.24
Past cocaine use disorder	3.9%	22.7%	10.3%	41.5%	<0.001	[4] > [2], [3] > [1]	0.83
Past meth use disorder	8.7%	34.1%	8.9%	35.9%	<0.001	[2], [4] > [1], [3]	0.003
Past opioid use disorder	3.5%	18.2%	3.5%	9.4%	<0.001	[2] > [1], [3]	0.79
Past sedative use disorder	0.4%	9.1%	1.1%	15.1%	<0.001	[2], [4] > [1], [3]	0.80
Disease							
Hepatitis C	17.0%	25.0%	17.3%	16.0%	0.62		0.07
AIDS status (% AIDS)	—	—	58.1%	58.5%	0.94		<0.001
Duration of HIV disease (yr)	—	—	9.3 (7.0)	9.0 (6.9)	0.62		0.10
cART status (% on)	—	—	71.5%	75.0%	0.46		0.01
Nadir $CD4^+$ T cell count,	—	—	190 (50, 300)	184 (40, 323)	0.50		<0.001
Current $CD4^+$ T cell count,	—	—	442 (268, 643)	475 (303, 665)	0.95		0.34
Plasma viral load (% detectable)	—	—	48.3%	46.2%	0.36		0.21
CSF viral load (% detectable)†	—	—	28.3%	26.9%	0.81		0.91

*Pairwise comparisons: proportion of people of color (Black, Latino, and other) to White.
†Missing values: data present for n = 506.
CAN+, cannabis exposure group; CAN−, noncannabis exposure group; PLHIV, people living with HIV; HIV−, people living without HIV; IQR, interquartile range.

(OR = 1.41, 95% CI = 0.63–3.16, $P = 0.40$) (Table 4, models 2a, 2b; Fig. 2). In analyses with the undetectable PLHIV sample and, separately, in the age-restricted sample (ages ≤65), controlling for the same covariates, findings in both subsamples showed a similar pattern to the whole sample analyses.

Cannabis on Cognitive Domains by HIV Status

Given cannabis exposure was related to lower odds of NCI among only PLHIV, we stratified groups by HIV status. Among PLHIV with relevant covariates and false discovery rate–adjusted *P* values, cannabis exposure was associated with higher performance in verbal fluency ($P = 0.02$, coefficient = 2.86) and learning ($P = 0.02$, coefficient = 2.70) domains, whereas among HIV− individuals, cannabis exposure was not significantly associated with any of the 7 cognitive domains.

DISCUSSION

Our findings present evidence that cannabis exposure was associated with lower odds of NCI in the context of HIV, although cannabis exposure showed no relation to NCI among HIV− individuals, consistent with our first

TABLE 3. Cannabis Use Characteristics of CAN+ Group (n = 150), Mean (SD) or Median (IQR)

	Overall cohort	HIV−	PLHIV	
		n = 44	n = 106	*P*
Age of first use	15.6 (5.0)	15.1 (4.7)	15.8 (5.1)	0.41
Mean lifetime grams/day	1.3 (1.8)	1.2 (1.7)	1.4 (1.8)	0.58
Days since last use	5 (1, 60.9)	10 (2, 109)	3 (1, 42)	0.09

CAN+, cannabis exposure group; HIV−, people living without HIV; PLHIV, people living with HIV; IQR, interquartile range.

hypothesis. We did not detect age as a moderating factor of cannabis nor HIV disease on NCI. Although cannabis exposure was associated with a lower proportion of NCI among PLHIV regardless of age, the magnitude of the association was not greater among older PLHIV compared with younger PLHIV, contrary to our second hypothesis. Our findings did not differ when the sample was restricted to undetectable PLHIV nor, separately, when the sample was restricted to ages 18–65 years. When cognitive performance was assessed by domain, cannabis exposure was associated with higher verbal fluency and learning performance only among PLHIV.

To the best of our knowledge, this is the first study to show that cannabis use was related to a lower odds of global NCI and better verbal and learning performance in the context of HIV disease in a large and racially/ethnically diverse cohort. Our results differ from previous work that has shown primarily null or adverse effects of cannabis on cognition in PLHIV[27,45,46] with adverse findings found selectively among frequent cannabis users (daily use, moderate-to-heavy users: 3+ times per day) and on specific cognitive domains (delayed recall, learning); furthermore, the adverse effects of cannabis on cognition identified by Cristiani et al (2004) were limited to PLHIV with symptomatic HIV disease. Chang et al (2006) observed no interactive effects between HIV disease and cannabis use (>4 days per week) on any neurocognitive test. Thames et al (2016) found global neurocognitive performance was similar among PLHIV and HIV− individuals who were light cannabis users (light users: at least weekly use, less than 2 times per day), and PLHIV light users showed better performance in verbal fluency compared with HIV− light users. The association between cannabis exposure and higher performance in verbal fluency in PLHIV is supported by the current study's findings. A clear methodological issue in the field of cannabis cognition research is differences in how cannabis exposure is defined, which may explain for some of the variation in outcomes. Given the small and mixed state of the literature, this study provides an important insight into the complex relationship of cannabis exposure and neurocognitive functioning in HIV.

Our results are consistent with the idea that under some circumstances, cannabis might be neuroprotective. If correct, possible mechanisms may involve the endocannabinoid modulatory effects of cannabis, which may mitigate some forms of neural injury in HIV disease. Studies of human and mouse cannabinoid systems in the context of neuroinflammatory exposures show that cannabinoid 2 receptors (CB_2) are highly upregulated during inflammatory insult and selective activation of CB_2 receptors reduces blood–brain barrier dysfunction,[24] vascular inflammation, and pathological microglial activation, thus indirectly decreasing oxidative stress, subsequent cell death,[47] and HIV-associated synapse loss.[48] Taken together, this literature cumulatively suggests there may be some therapeutic potential of compounds that target the cannabinoid system through modulation of neurotoxic and inflammatory processes in HIV disease and other neuroinflammatory diseases.[49,50] Given our findings did not differ in virally suppressed PLHIV, the anti-inflammatory effects of cannabis may be important for PLHIV who are both detectable and undetectable. For undetectable PLHIV, magnetic resonance spectroscopy biomarkers suggest that neuroinflammation and lower neuronal integrity persist despite virologic suppression on cART.[51]

Still, future research must further elucidate what levels of cannabis exposure are associated with optimal brain and neurocognitive health. For example, we are aware of at least one neuroimaging study specifically focusing on combined

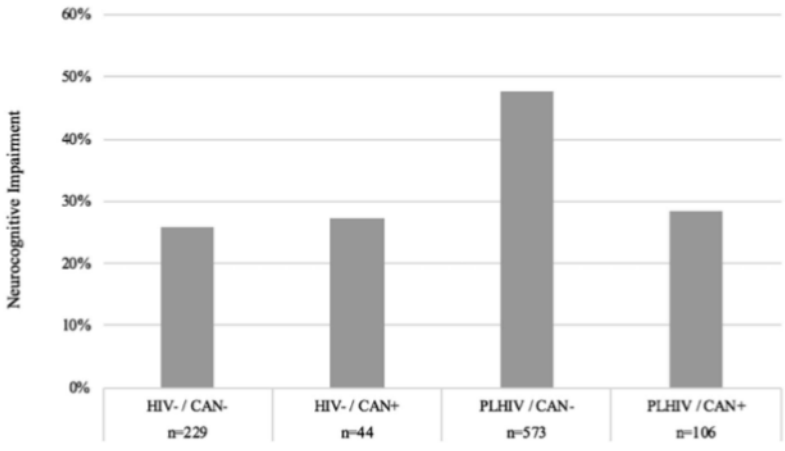

FIGURE 1. Rates of NCI stratified by HIV status (HIV−/PLHIV) and cannabis exposure (CAN−/CAN+). HIV–, People Living without HIV; PLHIV, People Living with HIV; CAN+, cannabis exposure group; CAN–, non-cannabis exposure group.

TABLE 4. Cannabis Exposure is Associated With Lower Probability of NCI in PLHIV

Variable	Odds Ratio (95% CI)	P
Model 1a: NCI (n = 952)		
Age	1.03 (1.01 to 1.05)	0.007
HIV+ (vs. −)	2.62 (1.84 to 3.75)	<0.001
CAN+ (vs. −)	1.07 (0.45 to 2.52)	0.87
Age × HIV	—	0.69
Age × CAN	—	0.10
HIV × CAN	—	0.14
Age × HIV × CAN	—	0.17
Model 1b: NCI (n = 952)		
Age	1.03 (1.01 to 1.05)	0.02
HIV+ (vs. −)	2.59 (1.82 to 3.69)	<0.001
CAN+ (vs. −)	1.25 (0.57 to 2.72)	0.57
Age × HIV	—	0.93
Age × CAN	—	0.10
HIV × CAN	—	0.045
Model 1c: NCI (n = 952)		
Age	1.02 (1.01 to 1.03)	<0.001
HIV+ (vs. −)	2.58 (1.82 to 3.66)	<0.001
CAN+ (vs. −)	1.43 (0.67 to 3.02)	0.35
HIV × CAN	—	0.02
Model 2a: NCI, stratified in HIV− (n = 273)		
CAN+ (vs. −)	1.41 (0.63 to 3.16)	0.41
Model 2b: NCI, stratified in PLHIV (n = 679)		
CAN+ (vs. −)	0.53 (0.33 to 0.85)	0.009

All models (1a,1b, 1c, 2a, and 2b) are adjusted for covariates: ethnicity/race, current major depressive disorder, and past methamphetamine use disorder; In models 1abc, the conditional effect of HIV disease is within the noncannabis exposure reference group and the conditional effect of cannabis exposure is within the HIV− reference group; HIV−, people living without HIV; PLHIV, people living with HIV; CAN+, cannabis exposure group; CAN−, noncannabis exposure group.

effects of cannabis exposure and HIV.[26] This study found that higher levels of cannabis exposure related to smaller entorhinal cortex and fusiform gyrus volumes, regardless of HIV status. Although further neuroimaging studies are needed to support conclusions, integrated findings from this study and those previously mentioned in this report suggest that cannabis exposure may only have beneficial effects on brain health up to a certain level of use, beyond which effects may be detrimental.

Next, given the lack of age effects observed in our analyses, one interpretation of our findings is that the effects of cannabis are protective for PLHIV across the age spectrum. However, it is also possible that our study was underpowered to detect an age X cannabis interaction due to the small sample size of older adults with cannabis exposure. Given these small numbers of older adults, the lack of differences in rates of cannabis use between younger and older adults in our study, the trend-level age X cannabis interaction, and the lack of age effects detected on rates of NCI should be interpreted with caution. As therapeutic and recreational use of cannabis compounds increases among older adults, future research examining these relationships specifically in larger samples of older adults (ages 60+) is warranted.

Study strengths include a large sample size of community-dwelling PLHIV and HIV− individuals. Although the racial/ethnic demographics of our cohort do not match the national PLHIV population (42% Black/African American, 23% Latino/Hispanic, 30% White, 5% other),[52] our PLHIV cohort does include substantial representation of Black/African American (n = 207, 30.5%) and Latino/Hispanic (n = 123, 18.1%) PLHIV who are disproportionately affected by HIV in the United States. In addition, our study used a comprehensive neuropsychological battery to assess cognitive functioning and used multiple tests to tap 7 domains of cognition, compared with previous studies which used brief cognitive batteries. Furthermore, our analyses controlled for more predictors of neurocognitive outcomes in PLHIV than previous studies, and our results remained significant even after controlling for covariates such as history of methamphetamine use disorder and current MDD, revealing a unique and robust contribution of cannabis exposure to neurocognitive outcomes in PLHIV. It is also of interest that the PLHIV/CAN+ group performed better neurocognitively despite having other risks that might have predicted the opposite (eg, greater frequency of past alcohol and cocaine use disorder).

These analyses are not without their limitations. Cross-sectional design precludes detection of casual effects from the observed associations between cannabis, HIV disease, and NCI. Longitudinal studies are necessary to determine the direction of effects between these exposures and outcomes. Although epidemiological studies show higher rates of cannabis use among PLHIV compared with the general population, our PLHIV and HIV− control group showed similar rates of cannabis exposure (current year cannabis use and past cannabis use disorder). This discrepancy with the literature is likely attributable to our research center's recruitment of HIV− individuals with similar levels of exposure to comorbid conditions (such as substance use and psychiatric disorders) as observed in our PLHIV cohort to provide an appropriate comparison group. Correspondingly, our HIV− cohort is not intended to be representative of the general population. This method of recruitment for our HIV− cohort may also explain the overall high rates of NCI observed in even the HIV−/CAN− group, as this group presents with higher levels of socioenvironmental exposures and conditions linked to NCI compared with the general population. To limit the influence of substances besides cannabis on our findings, we excluded recent noncannabis substance use disorders in the past year; however, as poly substance use is highly prevalent in our population, we considered as covariates rather than exclude for past lifetime history to increase the generalizability of our findings. A large proportion of the PLHIV cohort was not virally suppressed, which is partially attributable to lower rates of ART use, earlier ART regimes which were less potent and less well tolerated, and distinguishes this cohort from some other contemporary research HIV cohorts. To ensure that our study findings did not differ by detectable status, we conducted a subanalysis in the virally suppressed PLHIV cohort that

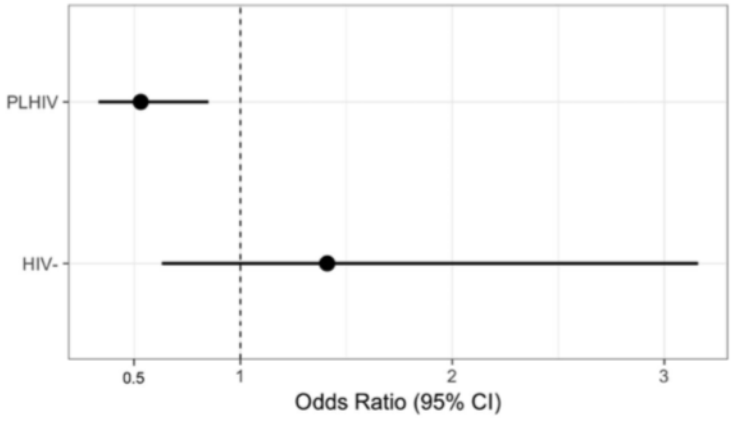

FIGURE 2. Odds ratios for effect of cannabis exposure on NCI in people living with HIV (n = 679) and HIV– individuals (HIV−) (n = 273). Cannabis exposure was associated with lower odds of NCI among PLHIV (OR = 0.53, 95% CI = 0.33 to 0.85, $P = 0.009$) and was not related to NCI among HIV− (OR = 1.41, 95% CI = 0.63 to 3.16, $P = 0.40$). Covariates were included in analysis but are not depicted in the figure.

showed a similar pattern of results. In terms of the generalizability of our PLHIV cohort, national epidemiological data show that only approximately 50% of PLHIV in the U.S. are virally suppressed due to disparities in the HIV care continuum.[53] Thus, the current study's rate of PLHIV with detectable plasma HIV RNA is generally representative of the U.S.'s PLHIV population. In addition, this study used retrospective self-report of cannabis use, which is vulnerable to inaccurate reporting, especially when reporting cannabis use from the remote past by our modified lifetime TLFB interview. We were also limited by using a categorical approach, which captured problematic use via cannabis use disorder diagnosis, and lacked detailed characterization of cannabis exposure.

Future investigations that capture the continuous and multidimensional spectrum of cannabis use, including the effects of dose, timing/frequency of use, and potency/composition of cannabis product [eg, Δ 9-tetrahydrocannabinol (THC) vs. cannabidiol (CBD) content], are needed to define a potential optimal neuroprotective range of cannabis use as well as define parameters of use that are neutral or harmful to neurocognition. Assessing contextual factors of cannabis use is critical to capturing the complexity of life conditions of individuals who use cannabis products and/or live with HIV and have been left unmeasured in many studies of cannabis use and neurocognition: psychosocial and socioeconomic context, motivations for cannabis use, and exposure to other substances and diseases. Future work from this research group aims to assess and investigate these factors. Although our study did not observe age modulating the relationship of cannabis use and neurocognition, older adults (ages 60+) represent an important and understudied group in the literature on the nonacute effects of cannabis on neurocognition, with few studies that show some null and mixed cannabis effects on cognitive domains in older adults.[17] To further probe the findings of the current study, investigation of mechanisms underlying potential neuroprotective effects of cannabis is of major interest via blood–brain barrier function, neuroimmune and neuroinflammatory processes, and gut microbiome signaling. The current study expands the available cannabis-neurocognition literature, suggests a link between cannabis exposure and a lower likelihood of NCI, and signals considerable future work is needed to clarify the parameters of cannabis' possible neuroprotective effects in brain structure/function and neurocognition among PLHIV across the lifespan.

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CHAPTER 2

Daily Cannabis Use is Associated with Lower CNS Inflammation in People with HIV

C. Wei-Ming Watson[1,2], Laura M. Campbell[1,2], Ni Sun-Suslow[1], Suzi Hong[1,3], Anya Umlauf[1], Ronald J. Ellis[1,4], Jenny Iudicello[1], Scott Letendre[5], Thomas D. Marcotte[1], Robert K. Heaton[1], Erin E. Morgan[1] & Igor Grant[1]

[1]Department of Psychiatry, University of California, San Diego; [2]San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology; [3]Department of Family Medicine and Public Health; [4]Department of Neurosciences, University of California, San Diego; [5]Department of Medicine, University of California San Diego

ABSTRACT

Objective: Recent cannabis exposure has been associated with lower rates of neurocognitive impairment in people with HIV (PWH). Cannabis' anti-inflammatory properties may underlie this relationship by reducing chronic neuroinflammation in PWH. This study examined relations between cannabis use and inflammatory biomarkers in cerebrospinal fluid (CSF) and plasma, and cognitive correlates of these biomarkers within a community-based sample of PWH.

Methods: 263 individuals were categorized into four groups: HIV– non-cannabis users (n = 65), HIV+ non-cannabis users (n = 105), HIV+ moderate cannabis users (n = 62), and HIV+ daily cannabis users (n = 31). Differences in pro-inflammatory biomarkers (IL-6, MCP-1/CCL2, IP-10/CXCL10, sCD14, sTNFR-II, TNF-α) by study group were determined by Kruskal-Wallis tests. Multivariable linear regressions examined relationships between biomarkers and seven cognitive domains, adjusting for age, sex/gender, race, education, and current CD4 count.

Results: HIV+ daily cannabis users showed lower MCP-1 and IP-10 levels in CSF compared to HIV+ non-cannabis users ($p = 0.015$; $p = 0.039$), and were similar to HIV– non-cannabis users. Plasma biomarkers showed no differences by cannabis use. Among PWH, lower CSF MCP-1 and lower CSF IP-10 were associated with better learning performance (all ps < 0.05).

Conclusions: Current daily cannabis use was associated with lower levels of pro-inflammatory chemokines implicated in HIV pathogenesis and these chemokines were linked to the cognitive domain of learning which is commonly impaired in PWH. Cannabinoid-related reductions of MCP-1 and IP-10, if confirmed, suggest a role for medicinal cannabis in the mitigation of persistent inflammation and cognitive impacts of HIV.

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Daily Cannabis Use is Associated With Lower CNS Inflammation in People With HIV

C. Wei-Ming Watson[1,2,*], Laura M. Campbell[1,2], Ni Sun-Suslow[1], Suzi Hong[1,3], Anya Umlauf[1], Ronald J. Ellis[1,4], Jennifer E. Iudicello[1], Scott Letendre[5], Thomas D. Marcotte[1], Robert K. Heaton[1], Erin E. Morgan[1] and Igor Grant[1]

[1]Department of Psychiatry, University of California, San Diego, USA
[2]San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology, San Diego, USA
[3]Department of Family Medicine and Public Health, University of California, San Diego, USA
[4]Department of Neurosciences, University of California, San Diego, USA
[5]Department of Medicine, University of California, San Diego, USA

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Abstract

Objective: Recent cannabis exposure has been associated with lower rates of neurocognitive impairment in people with HIV (PWH). Cannabis's anti-inflammatory properties may underlie this relationship by reducing chronic neuroinflammation in PWH. This study examined relations between cannabis use and inflammatory biomarkers in cerebrospinal fluid (CSF) and plasma, and cognitive correlates of these biomarkers within a community-based sample of PWH. **Methods:** 263 individuals were categorized into four groups: HIV− non-cannabis users ($n = 65$), HIV+ non-cannabis users ($n = 105$), HIV+ moderate cannabis users ($n = 62$), and HIV+ daily cannabis users ($n = 31$). Differences in pro-inflammatory biomarkers (IL-6, MCP-1/CCL2, IP-10/CXCL10, sCD14, sTNFR-II, TNF-α) by study group were determined by Kruskal–Wallis tests. Multivariable linear regressions examined relationships between biomarkers and seven cognitive domains, adjusting for age, sex/gender, race, education, and current CD4 count.
Results: HIV+ daily cannabis users showed lower MCP-1 and IP-10 levels in CSF compared to HIV+ non-cannabis users ($p = .015$; $p = .039$) and were similar to HIV− non-cannabis users. Plasma biomarkers showed no differences by cannabis use. Among PWH, lower CSF MCP-1 and lower CSF IP-10 were associated with better learning performance (all $ps < .05$). **Conclusions:** Current daily cannabis use was associated with lower levels of pro-inflammatory chemokines implicated in HIV pathogenesis and these chemokines were linked to the cognitive domain of learning which is commonly impaired in PWH. Cannabinoid-related reductions of MCP-1 and IP-10, if confirmed, suggest a role for medicinal cannabis in the mitigation of persistent inflammation and cognitive impacts of HIV.

Keywords: Neuroinflammation, cognition, neurocognitive impairment, marijuana, cannabinoids, NeuroAIDS, HIV/AIDS, cerebrospinal fluid

INTRODUCTION

HIV disease is associated with elevated immune system activation and persistent inflammation in the central nervous system (CNS) (Hong & Banks, 2015; Letendre, 2011). Neuroinflammatory responses persist despite virally suppressive antiretroviral therapy (ART) (Vera et al., 2016), and are likely major contributors to the pathogenesis of HIV-associated neurocognitive impairment (Gannon, Khan, & Kolson, 2011; Saylor et al., 2016). Although the prevalence of HIV-associated dementia has markedly decreased in the ART era, milder forms of neurocognitive impairment remain common, with a prevalence of 20–50% among people with HIV (PWH) (Iudicello et al., 2019; Saloner & Cysique, 2017). HIV-associated neurocognitive impairment has been associated with increased risk of deficits in real-world function including medication adherence, employment, automobile driving, and quality of life (Casaletto, Weber, Iudicello, & Woods, 2017). Interventions that target neuroinflammation underlying these cognitive difficulties are lacking currently, but burgeoning evidence suggests there are potential therapeutic benefits of cannabis (Manuzak et al., 2018; Rizzo et al., 2018).

Cannabis use is common among PWH in the U.S., with 23–56% reporting use in the past year (Pacek, Towe, Hobkirk, Nash, & Goodwin, 2018). PWH also frequently report using cannabis for medicinal purposes (25–35%)

*Correspondence and reprint requests to: Caitlin Wei-Ming Watson, M.S., HIV Neurobehavioral Research Program, 220 Dickinson Street, Suite B (8231), San Diego, CA 92103, USA. E-mail: c4watson@ucsd.edu

(Fogarty et al., 2007) primarily for pain relief, alleviation of anxiety and depression, and appetite stimulation (Woolridge et al., 2005). Randomized clinical trials of cannabis and cannabinoids show moderate evidence of clinical benefit for HIV-associated symptoms such as appetite/weight loss and sensory neuropathy (Ellis et al., 2009; National Academies of Sciences & Medicine, 2017; Whiting et al., 2015). Given high rates of use among PWH, growing state-based legalization in the U.S., and increased marketing of cannabis-based products, there is growing interest in examining the influence of cannabis on neurocognitive function in this population.

The current literature base examining the relationship of cannabis use and neurocognitive function in HIV shows inconsistent findings. Recent work from our group indicates that cannabis use is associated with lower rates of global neurocognitive impairment and higher performance in verbal fluency and learning domains selectively among PWH (Watson et al., 2020). Light cannabis-using PWH have also shown higher verbal fluency compared to HIV− light cannabis users (Thames, Mahmood, Burggren, Karimian, & Kuhn, 2016). Conversely, adverse effects of daily cannabis use on cognitive domains such as delayed recall/memory have also been observed (Cristiani, Pukay-Martin, & Bornstein, 2004), and several studies have shown comparable cognitive performance between PWH cannabis users and non-users (Chang, Cloak, Yakupov, & Ernst, 2006; Thames, Kuhn, Williamson, et al., 2017; Wang, Liang, Ernst, Oishi, & Chang, 2020). Such variable findings suggest that characteristics of cannabis usage such as frequency and quantity of use, as well as other contextual and cohort factors, likely moderate its effects on neurocognitive performance (Gonzalez, Pacheco-Colon, Duperrouzel, & Hawes, 2017).

Cannabis' anti-inflammatory properties may underlie the sometimes observed beneficial effect of cannabis exposure on neurocognitive function in HIV. Cannabis aside, inflammatory biomarker levels remain elevated in PWH and contribute to CNS injury even when HIV RNA levels are suppressed (Neuhaus et al., 2010; Wada et al., 2015). A key process in chronic HIV-associated neuroinflammation involves activated T-cell and monocyte migration to the brain. Subsequent interactions of infiltrating immune cells with astrocytes and microglia result in secretion of neurotoxic cytokines and chemokines (Hong & Banks, 2015; Ramesh, MacLean, & Philipp, 2013), and these pro-inflammatory factors in cerebrospinal fluid (CSF) and plasma have been related to worse neurocognitive performance in PWH (Burdo et al., 2013; Burlacu et al., 2020; Cohen et al., 2011; Imp et al., 2017; Kamat et al., 2012; Yuan et al., 2013).

Pre-clinical and human endocannabinoid system studies show that cannabinoids may mediate immunomodulatory actions that disrupt pro-inflammatory processes in HIV (Chen, Gao, Gao, Su, & Wu, 2017; Rom & Persidsky, 2013). Recent evidence has demonstrated associations between current cannabis use and reduced systemic inflammation among PWH, as indexed by lower levels of activated and inflammatory monocyte frequencies, and in plasma, lower levels of macrophage inflammatory protein (MIP)1α, interferon-gamma-inducible protein-10 (IP-10), also referred to as C-X-C motif chemokine ligand 10 (CXCL10), and tumor necrosis factor alpha (TNF-α) (Castro et al., 2019; Keen & Turner, 2015; Manuzak et al., 2018; Rizzo et al., 2018). In contrast, higher plasma levels of soluble cluster of differentiation 14 (sCD14) have been observed in cannabis-using compared to non-cannabis-using PWH (Castro et al., 2019), and many inflammatory plasma biomarkers (20 out of 21) have shown no differences by cannabis use among PWH (Manuzak et al., 2018). Higher levels of plasma interleukin-1β have also been observed among daily cannabis using PWH and HIV− individuals compared to non-users, with no differences in many inflammatory plasma biomarkers (23 out of 24) by cannabis use after controlling for multiple comparisons (Krsak et al., 2020). Thus, the prior literature is highly mixed, showing current cannabis use is associated with lower and higher levels of some plasma inflammatory biomarkers, and many peripheral markers show no evidence of cannabis-related modulation. No studies to date have examined the intersection of cannabis exposure, CNS inflammation, and cognition among PWH.

The goal of this study was to determine the relationship between cannabis use and HIV-associated inflammation, and the potential downstream association between inflammation and cognitive function. In study aim 1, we investigated the effects of no cannabis use, moderate cannabis use, and daily cannabis use on CSF and plasma biomarkers in PWH, with an HIV− non-cannabis-using comparison group. We hypothesized that cannabis use would be associated with lower levels of some inflammatory biomarkers among PWH, such as IP-10 and TNF-α, with others showing no differences by cannabis use, given the limited and mixed existing evidence. Post-hoc analyses investigated whether specific parameters of cannabis use over the past 6 months (cannabis quantity, cannabis recency, or cannabis frequency) correlated with CSF and plasma biomarkers.

In study aim 2, to determine the functional relevance of any anti-inflammatory cannabis effects observed, we first examined cognitive performance in PWH by cannabis use group, and next, examined relationships between inflammatory biomarker levels that were related to cannabis use in study aim 1, and cognitive performance in seven domains. We hypothesized that for biomarkers associated with cannabis use, lower levels of pro-inflammatory markers would relate to better performance in some cognitive domains among PWH, such as in verbal fluency and learning, based on previous findings from our group.

METHODS

Participants and Design

The sample included 263 community-dwelling adults enrolled in NIH-funded studies at UC San Diego's HIV Neurobehavioral Research Program (HNRP). Study design and cohort selection have been described in detail previously

(Heaton et al., 2011). Study visits took place between August 2001 and January 2018. All study procedures were approved by the UC San Diego Institutional Review Board. Participants provided written, informed consent.

Inclusion criteria for the current analyses were data present for (a) detailed self-report of cannabis and other substance use; (b) drug urine toxicology; (c) inflammatory biomarkers; and (d) neurocognitive and neuromedical assessments. Exclusion criteria for the parent studies included history of non-HIV-related neurological, medical, or psychiatric disorders that affect brain function (e.g., epilepsy, stroke, schizophrenia), learning disabilities, or a dementia diagnosis. Exclusion criteria for the current analyses were (a) positive urine toxicology for addictive substances other than cannabis; (b) report of any substance use disorder, including alcohol use disorder, in the past year other than cannabis; and (c) reported use of any of the following substances in the past year: cocaine, methamphetamine, amphetamine, other stimulants, heroin, other opioids, sedatives, anti-anxiety drug abuse, hallucinogens, PCP, ketamine, or inhalants.

Cannabis Use

Cannabis use was characterized by self-report and Δ^9-tetrahydrocannabinol (THC) positive urine toxicology. Frequency, quantity, and recency of cannabis use were assessed via a modified timeline follow-back (TLFB) interview (Robinson, Sobell, Sobell, & Leo, 2014). This modified TLFB captures age of first use and average quantities and frequencies of use during participant-identified periods of cannabis use. To define recent cannabis use patterns among participants, TLFB estimates were used to obtain an estimate of days since last use, as well as total days used, total grams used, and average grams per day of use, over the past 6 months.

Three cannabis use groups were defined for this study: non-cannabis users, moderate cannabis users, and daily cannabis users. When we initially examined cannabis use frequency within our cohort, this three-group categorization appeared to best characterize the natural distribution of cannabis use patterns. Non-cannabis users reported either no use of cannabis over their lifetime or no use in the past 5 years and had THC negative urine toxicology. Moderate cannabis users reported use of cannabis within the past month, with an average pattern of weekly use over the past 6 months (ranging from a minimum of 3 days of use over 6 months to a maximum of 3 days of use per week over 6 months), and could have positive or negative THC urine toxicology (given that participants with less frequent cannabis use could likely have a positive or negative THC screen on their testing day). Daily cannabis users reported a pattern of daily use over the past 6 months and had THC positive urine toxicology.

Inflammatory Biomarkers in CSF and Plasma

Blood was drawn via venipuncture through the antecubital vein into an EDTA vacutainer. Plasma was centrifuged at 1,800 relative centrifugal force for 8 min at room temperature and aliquoted for storage at −80°C until the time of assay. CSF was collected via lumbar puncture using a non-traumatic spinal needle and aseptic technique. CSF was centrifuged at low speed to separate cells; both supernatants and cells were aliquoted and stored at −80°C and were not thawed until the time of assay. Six pro-inflammatory biomarkers in plasma and CSF were measured using commercially available immunoassays and run according to the manufactures' protocol: Interleukin-6 (IL-6); monocyte chemoattractant protein-1 (MCP-1), also referred to as chemokine (C-C motif) ligand 2 (CCL2); IP-10; sCD14; soluble tumor necrosis factor receptor type II (sTNFR-II) and TNF-α. Biomarker precision was ensured by (a) assaying all specimens in duplicate; (b) repeating assays of specimens with coefficients of variation greater than 20%; (c) repeating 10% of all assays to assess operator and batch consistency; and (d) regularly assessing batch effects.

Neurocognitive Testing

Participants completed a standardized battery of well-validated neuropsychological tests designed to assess global cognition and seven domains: verbal fluency, executive function, attention/working memory, processing speed, learning, delayed recall/memory, and motor skills. Details about all tests included in this battery have been published elsewhere (Carey et al., 2004). Raw test scores were transformed into normally-distributed *t*-scores which are demographically adjusted for age, years of formal education, sex/gender, and race based on normative samples of HIV− participants (Heaton, Miller, Taylor, & Grant, 2004; Norman et al., 2011). Cognitive domain summary *t*-scores were generated by averaging *t*-scores across tests within a cognitive domain.

Neuromedical, Psychiatric, and Other Substance Use Assessment

Participants underwent a comprehensive neuromedical assessment. HIV infection was established by enzyme-linked immunosorbent assay with Western blot confirmation. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, and CD4 + T cells (flow cytometry) were performed. HIV viral load in plasma and CSF were measured using reverse transcriptase-polymerase chain reaction (Amplicor, Roche Diagnostics, Indianapolis, IN), with a lower limit of quantitation (LLQ) of 50 copies/ml. HIV viral load was dichotomized as detectable *versus* undetectable at the LLQ of 50 copies/ml. Detailed medical and antiretroviral usage history was captured via a structured, clinician-administered questionnaire. Current depression symptoms were assessed by the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996). Current tobacco use was assessed by a modified TLFB interview (Robinson et al., 2014), and defined by use (yes/no) in the past 6 months. Height and weight were used to calculate body mass index (BMI).

Statistical Analyses

Participants were categorized into four study groups based on HIV status and cannabis use: HIV− non-cannabis users, HIV+ non-cannabis users, HIV+ moderate cannabis users, and HIV+ daily cannabis users. Demographic, psychiatric, and HIV disease variables were compared across the four HIV/Cannabis groups using analysis of variance (ANOVA) or Kruskal–Wallis tests for continuous variables and χ^2 or Fisher's exact tests for categorical variables. Pair-wise comparisons were conducted to follow-up on significant omnibus results using Tukey's Honest Significant Difference (HSD) tests or Wilcoxon tests for continuous outcomes and χ^2 or Fisher's exact tests for categorical outcomes, with false discovery rate (FDR) adjustment. We also compared cannabis use characteristics between the HIV+ moderate and daily user groups (age of first use; over the past 6 months: total days used, total grams used, and average grams per day of use; days since last use; and THC positive urine toxicology).

For study aim 1, Kruskal–Wallis tests were used to compare levels of CSF and plasma biomarkers between the four HIV/Cannabis groups. *p*-values were adjusted using FDR correction for multiple comparisons, and *p*-values < .05 were considered statistically significant. Biomarkers were adjusted for batch effects and log10 transformed (except for sCD14) to improve fit and limit the influence of outliers. Additionally, non-parametric tests which are robust to outliers were employed for study aim 1. Biomarker data was further examined for outliers, defined as any log-transformed biomarker values outside the 3 SD range. Sensitivity analyses were conducted on a subset of participants, with all outliers identified by this criteria removed. Criteria for covariate inclusion in our study aim 1 models were characteristics that differed by cannabis use between the three HIV+ groups; all characteristics assessed showed comparable levels across HIV+ groups, and thus no covariates were included in study aim 1 models. Additional sensitivity analyses were conducted to examine whether including current tobacco use as a covariate influenced the relationship between cannabis use group and inflammatory biomarkers. In post-hoc analyses, Spearman's rho correlations examined whether specific parameters of cannabis use over the past 6 months (total grams of cannabis used, days since last cannabis use, or total days of cannabis use) correlated with inflammatory biomarkers.

For study aim 2, we first examined cognitive performance across HIV+ non-cannabis users, HIV+ moderate cannabis users, and HIV+ daily cannabis users. Next, multivariable linear regressions examined relationships between any biomarkers showing lower levels with cannabis use in study aim 1 and cognitive domain *t*-scores among PWH. Given that *t*-scores adjust for demographic factors that can influence cognitive performance: age, years of formal education, sex/gender, and race, we did not include any further demographic covariates in our models. We included current CD4 + T cell count and current tobacco use as covariates. Effect sizes for regression analyses were presented as estimated regression coefficients (b). *p*-values for the association of a biomarker with each cognitive domain were adjusted using FDR correction and *p*-values < .05 were considered statistically significant. Given that a portion of the HIV+ cohort was not virally suppressed, sensitivity analyses were conducted on a subset of PWH with undetectable plasma HIV RNA.

RESULTS

The study cohort of 263 community-dwelling adults included 198 PWH and 65 HIV− people, and ranged in age from 18 to 70 years old ($M = 42.3$, $SD = 11.1$). Four study groups included the HIV− non-cannabis users ($n = 65$) comparison group, and PWH categorized into three groups based on cannabis use: HIV+ non-cannabis users ($n = 105$), HIV+ moderate cannabis users ($n = 62$), and HIV+ daily cannabis users ($n = 31$).

Sample characteristics by HIV/Cannabis group are presented in Table 1. There were no significant differences in age, years of formal education, current tobacco use, nor hepatitis C virus across study groups. While there was a greater proportion of men, greater proportion of non-white people of color, higher depression symptoms, and lower BMI in the three HIV+ groups compared to the HIV− group, these characteristics did not differ between the HIV+ cannabis use subgroups. Thus, these characteristics were not included as covariates in study aim 1 models. Furthermore, no HIV disease characteristics (e.g. duration of HIV disease, current CD4 + T cell count, HIV RNA in plasma and CSF) differed across HIV+ cannabis use subgroups and were not included as covariates in study aim 1 models.

Self-reported cannabis use characteristics were compared between HIV+ moderate and daily cannabis users in Table 2. While age of first use was comparable between the two groups, over the past 6 months, daily users reported higher total days used, higher total grams used, and higher grams per day of use compared to moderate users ($p < .001$, $p < .001$, $p = .04$). Daily users reported a median of 0.5 grams per day of use (IQR = 0.2–1.1), while moderate users reported a median of 0.3 grams per day of use (IQR = 0.2–0.8). Per inclusion criteria for the daily users, 100% had THC positive urine toxicology, while 47.5% of moderate users had THC positive urine toxicology ($p < .001$).

CSF Biomarkers: Lower MCP-1 and IP-10 in Daily Cannabis Users

Kruskal–Wallis tests revealed a significant omnibus difference across HIV/Cannabis groups in MCP-1 and IP-10 levels in CSF ($p = .027$; $p = .001$) with FDR adjustment. Follow-up pair-wise comparisons showed that MCP-1 and IP-10 levels in CSF were significantly lower in HIV+ daily cannabis users compared to HIV+ non-cannabis users ($p = .015$; $p = .039$; Figure 1A and 1B). Furthermore, CSF MCP-1 was higher in HIV+ non-cannabis users compared to the HIV− non-cannabis users ($p = .005$; Figure 1A). CSF IP-10 was higher in HIV+ non-cannabis and moderate cannabis users compared

Table 1. Sample characteristics ($n = 263$)

Characteristic	HIV− Non-cannabis users ($n = 65$)	HIV+ Non-cannabis users ($n = 105$)	HIV+ Moderate cannabis users ($n = 62$)	HIV+ Daily cannabis Users ($n = 31$)	p-value
Demographics					
Age (years)	44.9 (11.7)	40.2 (10.9)	43.3 (10.8)	42.0 (10.5)	ns
Education (years)	13.6 (2.4)	13.6 (2.9)	13.7 (2.3)	13.0 (2.9)	ns
Sex/gender (% men)[1]	67.7%	81.9%	95.2%	87.1%	.004
Race/ethnicity[1]					.008
White	66.2%	41.0%	58.1%	38.7%	
Black	15.4%	22.9%	19.4%	38.7%	
Latino	18.5%	30.5%	14.5%	19.4%	
Asian	0%	1.9%	1.6%	3.2%	
Other	0%	3.8%	6.5%	0%	
HIV disease					
Duration of HIV (years)		7.2 (1.8–15.8)	9.4 (2.2–16.1)	6.3 (3.6–14.6)	ns
Nadir CD4 + T cells		227 (89–385)	175 (40–318)	203 (48–388)	ns
Current CD4 + T cells		479 (323–687)	505 (294–681)	506 (378–761)	ns
ART status (% on)		66.7%	80.7%	74.2%	ns
Total ART duration (years)		4.9 (5.4)	5.1 (4.7)	4.6 (4.2)	ns
HIV RNA in plasma (% undetectable)		71.4%	77.1%	60.9%	ns
HIV RNA in CSF (% undetectable)		90.0%	92.0%	95.5%	ns
Psychiatric, Substance use, Medical					
Depression (BDI-II score)[1]	1.5 (0–7.3)	10 (4–16)	8.5 (4–16.8)	12 (4–22)	<.001
Current tobacco use[2]	23.1%	26.7%	35.5%	35.5%	ns
BMI	30.0 (6.9)	27.0 (4.9)	26.5 (4.5)	25.7 (5.1)	<.001
Hepatitis C virus	12.3%	8.7%	11.7%	10.0%	ns

Data are presented as Mean (*SD*), Median (IQR), or %.
Abbreviations: ns = non-significant ($p \geq .05$); HIV = human immunodeficiency virus; ART = antiretroviral therapy; BDI-II = Beck Depression Inventory-2nd Edition; BMI = Body Mass Index.
[1] Only four characteristics varied between the four groups: sex/gender, race/ethnicity, depression symptoms, and BMI. All three HIV+ groups had a higher proportion of men and people of color, higher depression symptoms, and lower BMI compared to the HIV− group but these variables did not differ by cannabis use between HIV+ groups.
[2] Use in the past 6 months.

Table 2. Cannabis use characteristics of HIV+ moderate and daily users

Characteristic	Moderate cannabis users ($n = 62$)	Daily cannabis users ($n = 31$)	p-value
Age of first use	16.8 (4.9)	15.4 (4.0)	ns
Total days used[1]	18 (6–37)	180 (171–180)	<.001
Total grams used[1]	6 (2–19)	90 (36–165)	<.001
Average grams per day[1,2]	.3 (0.2–0.8)	.5 (0.2–1.1)	.04
Days since last use	3 (1.0–9.5)	1 (0.5–1.0)	<.001
THC+ urine toxicology	47.5%	100.0%	<.001

Data are presented as Mean (*SD*) or Median (IQR).
Abbreviations: ns = non-significant ($p \geq .05$); HIV = human immunodeficiency virus; THC = Δ9-tetrahydrocannabinol.
[1] Over the past 6 months.
[2] Per day of cannabis use.

to the HIV− non-cannabis users ($p < .001$, $p = .003$; Figure 1B). No differences were observed in IL-6, sCD14, sTNFR-II, and TNF-α levels in CSF across HIV/Cannabis groups.

Plasma Biomarkers: No Differences by Cannabis Use

Plasma biomarkers IL-6, MCP-1, sCD14, sTNFR-II, and TNF-α showed no significant omnibus differences across HIV/Cannabis groups. There was a significant omnibus difference across HIV/Cannabis groups in plasma IP-10 levels ($p < .001$) with FDR adjustment. Follow-up pairwise comparisons showed that plasma IP-10 was elevated in all three HIV+ groups: HIV+ non-cannabis users ($p < .001$), HIV+ moderate cannabis users ($p < .001$), and HIV+ daily cannabis users ($p = .042$), compared to the HIV− group.

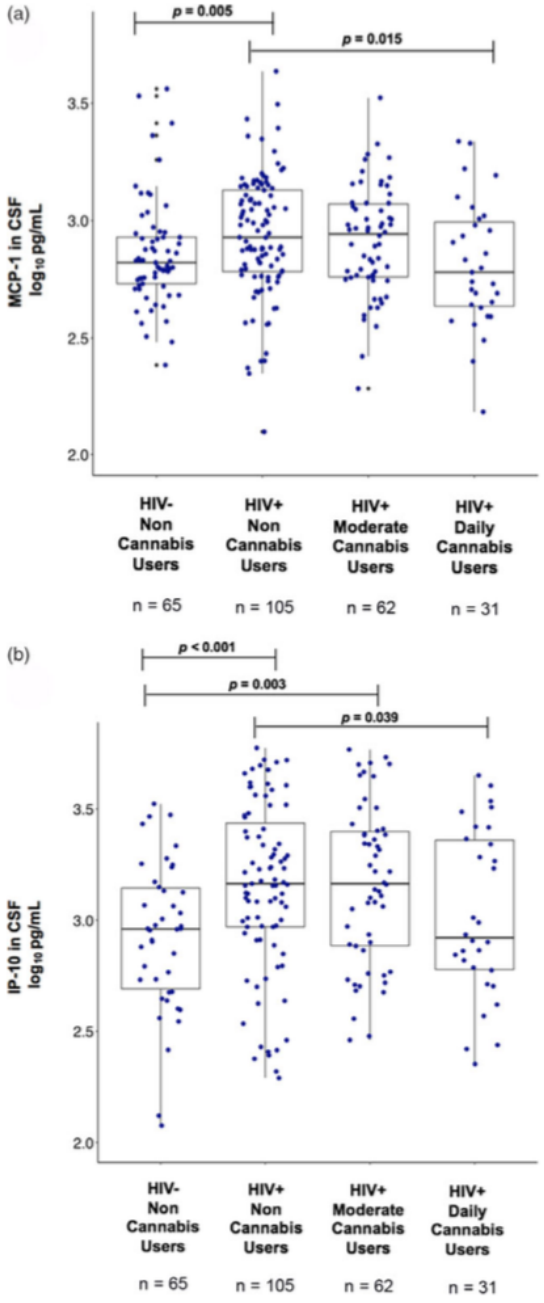

Fig. 1. HIV+ daily cannabis users display lower levels of MCP-1 and IP-10 in CSF compared to HIV+ non-cannabis users. Abbreviations: MCP-1 = monocyte chemoattractant protein-1; IP-10 = interferon-gamma-inducible protein-10; CSF = cerebrospinal fluid; HIV = human immunodeficiency virus

In sensitivity analyses with biomarker outliers removed, CSF and plasma findings did not differ from whole sample analyses. In sensitivity analyses adjusting for current tobacco use, CSF and plasma findings also did not differ from whole sample analyses, and no independent effects of tobacco use on CSF or plasma biomarker levels were observed.

Cannabis Use Parameters and Biomarker Correlations

Total grams of cannabis used over the past 6 months did not correlate significantly with any CSF or plasma biomarkers ($ps > .05$). Days since last cannabis use also did not correlate significantly with any CSF or plasma biomarkers ($ps > .05$). Two trend-level correlations were observed. Total grams of cannabis used trended towards a small to medium negative correlation with CSF IP-10 ($r = -.19$, $p = .083$), indicating that more grams consumed was weakly linked to lower IP-10 in CSF. Days since last cannabis use trended towards a small to medium positive correlation with CSF MCP-1 ($r = .18$, $p = .082$), indicating more recent cannabis use was weakly linked to lower MCP-1 in CSF. Total days of cannabis use over the past 6 months had medium and significant negative correlations with CSF MCP-1 ($r = –.23$, $p = .026$) and CSF IP-10 ($r = –.27$, $p = .011$), indicating that greater days of cannabis use predicted lower levels of MCP-1 and IP-10 in CSF.

Cognitive Performance and CSF MCP-1 and IP-10

Across the HIV+ groups, HIV+ daily cannabis users had similar global cognitive performance with a trend of better performance ($M = 48.8$, $SD = 6.0$) compared to HIV+ moderate cannabis users ($M = 46.4$, $SD = 6.5$) and HIV+ non-cannabis users ($M = 46.9$, $SD = 6.8$) ($p = .26$). An analogous pattern was observed in the domains of: verbal fluency, attention/working memory, processing speed, learning, and motor skills, with a slightly and non-significantly higher performance among HIV+ daily cannabis users. Among all PWH, a negative association was detected between MCP-1 in CSF and learning performance ($\beta = -6.3$, $p = .016$; Table 3), indicating that lower MCP-1 is related to better learning, while adjusting for current CD4 count and current tobacco use. A negative association was also detected between IP-10 in CSF and learning ($\beta = -2.3$, $p = .036$; Table 3) among PWH, indicating that lower IP-10 was associated with better learning performance with the same covariate and FDR adjustment. CSF MCP-1 and IP-10 did not relate significantly to any other cognitive domains among PWH.

In sensitivity analyses with the PWH sample restricted to those with undetectable plasma HIV RNA viral load, CSF and plasma biomarker and cognitive domain findings (study aims 1 and 2) did not differ from whole sample analyses.

DISCUSSION

Study findings support our hypotheses that frequent cannabis exposure may reduce neuroinflammation in PWH, with possible downstream benefits for cognition. Daily cannabis use

Table 3. Relationship of CSF biomarkers and cognitive domains among people with HIV

	MCP-1		IP-10	
Cognitive Domain	β (*SE*)	*p*-value[1]	β (*SE*)	*p*-value[1]
Verbal Fluency	−2.1 (2.6)	ns	−1.2 (1.3)	ns
Executive Function	−2.4 (2.8)	ns	−1.2 (1.5)	ns
Attention/Working Memory	−3.8 (2.6)	ns	.1 (1.3)	ns
Processing Speed	−3.1 (2.7)	ns	−.3 (1.4)	ns
Learning	−6.3 (2.6)	.016	−2.3 (1.4)	.036
Delayed Recall/Memory	−3.9 (2.6)	ns	−1.9 (1.4)	ns
Motor	−2.3 (3.0)	ns	−.2 (1.6)	ns

Cognitive *t*-scores are adjusted for age, sex/gender, race, and years of formal education, and models adjust for current tobacco use and current CD4 + T cell count.
Abbreviations: ns = non-significant ($p \geq .05$); CSF = cerebrospinal fluid; HIV = human immunodeficiency virus; MCP-1 = monocyte chemoattractant protein-1; IP-10 = interferon-gamma-inducible protein-10.[1] *p*-values were adjusted using false discovery rate (FDR) correction for multiple comparisons.

was associated with lower levels of pro-inflammatory chemokines MCP-1 and IP-10 in CSF, factors critical to immune cell migration and HIV pathogenesis. In contrast, cannabis use was not associated with inflammatory biomarker levels in plasma. HIV+ daily cannabis users showed similar cognitive performances with a trend toward higher scores in global cognition and several cognitive domains including learning compared to HIV+ moderate users and HIV+ non-cannabis users. Lower CSF levels of MCP-1 and IP-10 were related to better cognitive performance in the domain of learning, which is commonly impaired in HIV disease. When recent cannabis use parameters were examined, cannabis quantity and cannabis recency did not correlate significantly with any inflammatory biomarkers, but greater total days of cannabis use, or cannabis frequency, significantly predicted lower levels of MCP-1 and IP-10 in CSF. Findings indicate that regular, daily cannabis use may be important for reduced CNS inflammation in HIV. Importantly, daily cannabis users in this cohort reported a median of half a gram of cannabis use per day, and 75% of daily users reported less than 1.1 grams of cannabis use per day, suggesting that frequent, but not heavy cannabis use generally characterized this group. Therefore, inference about the anti-inflammatory benefit of cannabis in PWH cannot be extrapolated to more high-dose, heavy use of cannabis. Furthermore, given our study design is retrospective and cross-sectional, we cannot clarify actual cause-effect relationships regarding the inflammation modulatory effects of cannabis, which would require longitudinal study design.

Our study findings are novel in detection of lower pro-inflammatory chemokines with cannabis exposure specifically in CSF, and converge with recent research showing anti-inflammatory activity of cannabis in PWH on activated immune cells and systemic inflammation (Manuzak et al., 2018; Rizzo et al., 2018). Lower CSF MCP-1 and IP-10 with daily cannabis use and no differences by cannabis use for CSF biomarkers IL-6, sCD14, sTNFR-II, and TNF-α suggest that MCP-1 and IP-10 may be specifically sensitive to cannabis-related modulation and could play a mechanistic role in any downstream cognitive benefit or physical symptom relief observed with regular cannabis use among PWH. Both IP-10 and MCP-1 are considered important contributors to neuroinflammation in HIV infection and reductions in their levels could have beneficial downstream effects for PWH. IP-10 is a major chemo-attractant for T-cells and activated monocytes, and in excess, leads to neurotoxic pro-inflammatory cytokine production and neuronal apoptosis, while MCP-1 mediates trafficking of infected macrophages across the blood brain barrier (Asensio et al., 2001; de Almeida et al., 2005; Pulliam et al., 2011; Simmons et al., 2013). Our findings suggest that cannabis use may lead to reduced CNS-infiltration of T cells and monocytes. In a small pilot study, our group recently reported that cannabis recency (days since last use) was associated with lower levels of CSF interleukin-16 (IL-16) and C reactive protein (CRP) (Ellis, Peterson, Li, et al., 2020). These findings are complementary with the current study in suggesting that sustained reductions in neuroinflammation related to cannabis likely require ongoing exposure, although we only observed a small to medium and non-significant relationship between cannabis recency and CSF MCP-1 in this cohort. The current study's findings suggest that the parameter of cannabis frequency is slightly more predictive of inflammatory biomarker levels compared to cannabis quantity and cannabis recency. An additional benefit of cannabis, potentially linked to its anti-inflammatory effects, is stabilization of the blood brain barrier, which we demonstrated in a separate report showing that more frequent use of cannabis in the past month was associated with higher blood brain barrier integrity in PWH (Ellis, Peterson, Cherner, et al., 2020). We extend this work in the current study, showing that lower MCP-1 and lower IP-10 relate to better learning performance, a cognitive domain which frequently shows mild deficits in PWH in the ART era (Heaton et al., 2010). Elevated MCP-1 and IP-10 in CSF have previously been observed in PWH with HIV-associated neurocognitive disorder (Mehla, Bivalkar-Mehla, Nagarkatti, & Chauhan, 2012; Yuan et al., 2013).

Taken together, findings are consistent with the notion that cannabinoids may modulate inflammatory processes in PWH, specifically in the CNS, and suggest a link between

lower CNS inflammation and better neurocognitive function. Our finding that HIV+ daily cannabis users showed slightly and non-significantly better performance in several cognitive domains compared to HIV+ non-users reflects a similar pattern to a recent study (Wang et al., 2020), suggesting a signal of a neuroprotective effect which warrants further investigation of regular cannabis use among PWH. Our sensitivity analyses indicate that the relationships observed between cannabis, inflammatory biomarkers, and cognition are relevant to PWH with both detectable and undetectable plasma HIV RNA.

In plasma, we observed elevated IP-10 in all three HIV+ groups compared to the HIV− group, but we did not detect lower levels of plasma IP-10 nor TNF-α with cannabis use as previous studies found (Keen & Turner, 2015; Rizzo et al., 2018). Our null findings for the relationship between cannabis use and plasma biomarker levels are congruous with several other studies in which the vast majority of peripheral inflammatory and immune activation markers show no differences by cannabis use (Castro et al., 2019; Krsak et al., 2020; Manuzak et al., 2018). Although plasma levels of chemokines such as MCP-1 are generally reflective of inflammatory states and found to be elevated in patients with neurodegenerative diseases (Lee et al., 2018), chemokine levels in the CNS may more specifically indicate their role in microglial activation and proliferation and chemotaxis of blood monocytes to the CNS (Weiss, Downie, Lyman, & Berman, 1998). It is important to recognize the biological implications of differing chemokine levels found in CSF and plasma hence, differential cannabis effects. There may be several reasons why we observed distinct cannabis effects in CSF and plasma. Cannabinoids are highly lipid soluble, so their biological effects may be amplified and prolonged in CSF as compared to blood (Hložek et al., 2017; Huestis & Smith, 2007). Furthermore, immune responses between CNS and peripheral blood are typically compartmentalized and the dynamics of chemokine production, degradation, and removal in each may differ. Numerous HIV studies have shown that levels of neurotoxic chemokines such as MCP-1 and IP-10 are much higher in CSF than in plasma, suggesting that there are distinct production and metabolism processes for these chemokines in CSF compared to plasma (de Almeida et al., 2005; Yuan et al., 2015). Although we cannot determine the exact cellular sources of MCP-1 in CSF in our study, MCP-1 causes activation and proliferation of microglia and neurotoxicity, highlighting its role in neuroinflammation and brain outcomes (Hinojosa, Garcia-Bueno, Leza, & Madrigal, 2011; Yang et al., 2011). Lastly, CSF biomarkers may be more robust indicators of changes relevant to CNS function and neurocognitive outcomes compared to peripheral blood markers.

Mechanistically, our findings are consistent with the current preclinical literature showing cannabis-related modulation of pro-inflammatory processes in HIV via the endocannabinoid system (Costiniuk & Jenabian, 2019). While cannabinoid type 1 (CB1) receptors are the principal type found in the CNS and account for the psychoactive effects of ligands such as THC, cannabinoid type 2 (CB2) receptors also are expressed in the CNS by microglia and astrocytes (Bisogno & Di Marzo, 2010; Van Sickle et al., 2005). Preclinical models show activation of CB1 and CB2 receptors can induce apoptosis of activated T-cells and macrophages (Persidsky et al., 2015), downregulate pro-inflammatory cytokine and chemokine production (Nagarkatti, Pandey, Rieder, Hegde, & Nagarkatti, 2009), and inhibit HIV-associated synapse loss and neural injury (Kim, Shin, & Thayer, 2011; Ramirez et al., 2013). Both natural and synthetic cannabinoids have demonstrated neuroprotective effects after various types of CNS insults, and in particular under conditions of high inflammation (Bilkei-Gorzo et al., 2017; Chen et al., 2017). In vitro, THC treatment has been shown to suppress a number of pro-inflammatory factors including TNF-α, IL-6, and IL-8 and decrease NF-κB secretion in human osteosarcoma cells (Yang, Li, Han, Jia, & Ding, 2015) as well as monocyte-derived interleukin IL-1β production and astrocyte secretion of MCP-1 and IL-6 from a human coculture system (Rizzo et al., 2019). In sum, there is substantial evidence that cannabinoids display beneficial effects on chronic inflammatory responses in HIV infection.

Our study has several limitations. First, cross-sectional analyses of an observational cohort cannot establish cause–effect relationships. Second, we lacked an HIV− cannabis user group to compare cannabis effects on inflammatory markers by HIV status. While an HIV− cannabis-using group would allow for a more balanced design, our HIV− non-cannabis user group did allow us to observe differences in inflammatory markers between this comparison group and the three HIV+ cannabis use groups. Third, the majority of participants in this study were men and we were underpowered to examine sex/gender differences or similarities in cannabis-related modulation of inflammatory markers. Animal models have shown that endogenous sex hormones and synthetic steroid hormones influence physiological response to cannabinoids, and modulate drug sensitivity (Struik, Sanna, & Fattore, 2018), and a recent study among PWH suggests a few inflammatory biomarker levels differ by sex/gender (Rubin et al., 2019). Future work should include a larger cohort of women with HIV and examine whether relationships between cannabis, neuroinflammation, and cognition are similar or vary by sex/gender or by specific hormone levels. Fourth, our method of defining cannabis use groups combined self-report of frequency and quantity of use and urine toxicology. While this method is more comprehensive than most previous studies in PWH, which rely solely on self-report, self-report of drug use remains prone to inaccuracy due to possibility of recall bias and/or social desirability bias. Previous studies have collected more detailed frequency of use data with the number of times of cannabis use per day to characterize heavier user groups (Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Thames et al., 2016) while our study only characterized daily users. Further, two recent studies used a more precise method to categorize levels of cannabis exposure with direct measurement of cannabis metabolites in plasma (Manuzak et al.,

2018; Rizzo et al., 2018); this data is not available for our sample. Additionally, we did not collect information concerning important aspects of cannabis use such as: recreational *versus* medicinal use, cannabinoid composition (e.g. THC/CBD ratio), nor strength of cannabis strain. Such contextual variables may moderate the anti-inflammatory effects of cannabis observed in this study. Fifth, our study lacks data on anxiety disorders, post-traumatic stress disorder (PTSD) and numerous forms of social adversity that PWH commonly face in the U.S. and are detrimental to neurocognition (Rubin et al., 2017; Thames, Kuhn, Mahmood, et al., 2017; Watson et al., 2019). Lastly, our study did not collect standardized data on dietary factors nor regular physical exercise which can influence chemokine expression via pro-inflammatory or anti-inflammatory effects (Montoya et al., 2019). Future cannabis research in PWH should undertake careful assessment of cannabis use, anxiety and trauma-related disorders, social adversity, and dietary and physical exercise variables, as these factors should be considered for their influence on both inflammatory processes and neurocognitive outcomes.

Future studies in PWH are needed to investigate potential distinct effects of specific cannabinoids, and adult medicinal use, on brain structure and function. These relations among PWH can be clarified in longitudinal studies following designs of recent medicinal cannabis, neuroimaging, and cognition studies in a general clinical population (Gruber et al., 2018). Any neuroprotective effects of cannabis products on cognition are likely limited to specific cannabis/cannabinoid use parameters and individual characteristics of users (disease comorbidities, pharmacokinetic factors). In the general population, studies of heavy recreational cannabis use and cannabis dependence show CB1 receptor downregulation, which may be a mechanism for drug tolerance, lead to CB2 receptor desensitization on immune cells, and disrupt endocannabinoid system homeostasis (Hirvonen et al., 2012; Rotter et al., 2013). Thus, determination of harmful levels of cannabis use in relation to quantity and addictive potential must be considered in PWH.

Our work demonstrated some reduced inflammation in CSF, but not plasma, among HIV+ daily cannabis users who reported a median of half a gram of cannabis use per day. Of functional relevance, lower levels of chemokines MCP-1 and IP-10 in CSF were associated with better cognitive performance in the domain of learning among PWH. Our findings point to the need for more targeted mechanistic studies of cannabis use and cognition specifically in PWH. In the context of HIV-associated chronic immune system activation and neuroinflammation, cannabis-based therapeutics may have a role in reducing inflammation and risk for downstream neurocognitive impairment.

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CONFLICT OF INTEREST

The authors have nothing to disclose.

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CHAPTER 3

A Longitudinal Study of Cannabis Use and Risk for Cognitive and Functional Decline among Older Adults with HIV

C. Wei-Ming Watson[1,2], Erin Sundermann[1], Jonathan Helm[2,3], Emily W. Paolillo[1,2], Suzi Hong[4], Ronald J. Ellis[1,5], Scott Letendre[6], Thomas D. Marcotte[1], Robert K. Heaton[1], Erin E. Morgan[1] & Igor Grant[1]

[1]Department of Psychiatry, University of California, San Diego; [2]San Diego State University/University of California, San Diego Joint Doctoral Program in Clinical Psychology; [3]Department of Psychology, San Diego State University; [4]Department of Family Medicine and Public Health, University of California San Diego; [5]Department of Neurosciences, University of California San Diego; [6]Department of Medicine, University of California San Diego

ABSTRACT

Objective: Cannabis use is rapidly increasing among older adults in the United States, in part to ameliorate symptoms of common health conditions. Longitudinal studies of cannabis use and cognitive decline in aging populations living with chronic disease are lacking. We examined different levels of cannabis use and cognitive and everyday function over time among older adults with HIV.

Methods: 297 older adults with HIV (ages 50–84 at baseline) were followed longitudinally for up to 10 years (average years of follow-up=3.9). Participants were classified based on average cannabis use across study follow-up: frequent (>weekly) (*n*=23), occasional (≤weekly) (*n*=83), and non-cannabis users (*n*=191). Multi-level models examined the effects of average and recent cannabis use on global cognition, global cognitive decline, and functional independence.

Results: Occasional cannabis users showed better global cognitive performance compared to non-users (*b*=0.50, *p*=0.03). Rates of cognitive decline and functional problems did not vary by average cannabis use. Recent cannabis use was linked to worse cognition at study visits when participants had THC+ urine toxicology (*b*=–0.27, *p*=0.03); this was driven by worse memory, but did not extend to concurrent declines in everyday function.

Conclusions: Occasional (≤weekly) cannabis use is associated with better global cognition over time in older adults with HIV, a group vulnerable to chronic inflammation and

cognitive impairment. Recent THC exposure may have a temporary adverse impact on memory. To inform safe and efficacious medical cannabis use, the effects of specific cannabinoid doses on cognition and biological mechanisms must be investigated in older adults.

Introduction

Cannabis is the third most prevalent substance used by older adults (≥50 years), after alcohol and tobacco, and cannabis use is increasing among older adults faster than any other age group in the United States (Han & Palamar, 2018; Kuerbis, Sacco, Blazer, & Moore, 2014; Lloyd & Striley, 2018). This trend is expected to continue (Han & Palamar, 2020) given the expansion of state-based medical and recreational legalization, shifting cultural attitudes, and the widespread marketing of cannabis products to treat a host of conditions. There is an urgent public health need to identify risks and benefits of cannabis use in this population, as well as individual-level and cannabis-level factors that may moderate its effects (Minerbi, Häuser, & Fitzcharles, 2019). In particular, there is growing interest in clarifying the influence of cannabis use on cognitive function in aging populations living with chronic disease, who are vulnerable to cognitive decline and late-life dementias such as Alzheimer's disease (Sagar & Gruber, 2018; Scott et al., 2019).

Older adults are more likely to use cannabis for medical purposes compared to younger populations (Choi et al., 2017), and mixed medical/recreational use is also reported (Sexton et al., 2019). Older cannabis users are also more likely to use products with higher cannabidiol (CBD) content and lower Δ^9-tetrahydrocannabinol (THC) content compared to younger age groups. Older adults report they use cannabis to ameliorate a range of health conditions common in aging, with those most frequently endorsed including chronic pain, sleep disturbances, weight loss, anxiety, and depression (Hazekamp et al., 2013). However, robust evidence to support therapeutic benefit of cannabis products on these conditions is limited (Minerbi et al., 2019; National Academies of Sciences & Medicine, 2017). Age-related changes such as slowed metabolism and high rates of polypharmacy may complicate safe and efficacious medical

cannabis use, increasing drug sensitivity and risk for drug-drug interactions. Acute sedation and dizziness have been observed in older cannabis users, which could increase fall risk (van den Elsen et al., 2014). National survey data show older adults who use cannabis medically are more likely to report functional impairments, while recreational cannabis use did not predict reports of such impairment. Authors hypothesized that functionally-impairing symptoms may have motivated initiation of medical cannabis use, but could not determine whether cannabis use also exacerbated functional problems such as impaired thinking and walking (Han, Le, Funk-White, & Palamar, 2021).

Recent reviews highlight the scarcity of research that directly examines the effect of late-life cannabis use on cognitive health and brain aging (Pocuca, 2020; Scott et al., 2019; Weinstein & Sznitman, 2020). Only one cross-sectional study (n = 38, ages 60–80) examined *current* cannabis use and cognitive performance in a healthy older adult cohort, finding no cognitive differences by cannabis use, but analyses were underpowered (Thayer et al., 2019). Two other cross-sectional studies found no association between heavy cannabis use in adolescence and late-life cognitive performance (n = 50, ages 58–72) (Burggren et al., 2018), or between active cannabis use at age 42 and cognitive performance at age 50 (n = 8,992) (Dregan & Gulliford, 2012). Two mid-life cohort studies have linked current ≥weekly cannabis use (n = 1,897) and separately, greater cumulative cannabis exposure over adulthood (n = 3,385) to a small decrement in verbal memory performance, which was not considered clinically significant (Auer et al., 2016; McKetin et al., 2016). Longitudinal analyses showed no differences by cannabis use in verbal memory rates of change over eight years (McKetin et al., 2016); however, there was no evidence of cognitive decline in this mid-life cohort. In contrast to these findings, in small intervention studies (n = 22, n = 11), adults showed improvements in executive functioning after

initiation of medical cannabis use (Gruber et al., 2018; Gruber et al., 2016). Study findings suggest that medicinal users experience physical symptom relief, improvements in mood and function, and reductions in prescription opioid and benzodiazepine use, which authors hypothesize could contribute indirectly to better cognition. In sum, the current evidence is inadequate to address whether cannabis use is a risk factor for cognitive decline in aging populations, and it appears cannabis may demonstrate divergent effects at specific levels and contexts of use.

Growing evidence from animal studies and investigation of the human body's natural endocannabinoid system show that cannabinoids (e.g. chronic low dose THC) demonstrate anti-inflammatory and neuroprotective effects (Bilkei-Gorzo et al., 2017; Cristino, Bisogno, & Di Marzo, 2020). While there is no research in humans to suggest cannabis compounds decrease risk for cognitive decline, there is interest in examining the therapeutic potential of cannabinoid products on brain function under conditions of high inflammation (Whiting et al., 2015). For older adults with pro-inflammatory health conditions such as HIV, late-life cannabis use may exert distinct effects on cognition. In HIV, chronic inflammation and immune system activation persist despite virally suppressive antiretroviral therapy (ART), and elevated immune biomarkers have been linked to greater cognitive impairment (Harezlak et al., 2011; Hong & Banks, 2015). Older adults with HIV show steeper rates of cognitive decline compared to their older HIV-negative counterparts (Canizares, Cherner, & Ellis, 2014), and the immunomodulatory properties of cannabis may be particularly beneficial in this context. *In vitro* studies show activation of cannabinoid receptors attenuates HIV replication in T-cells, microglia, and macrophages (Ramirez et al., 2013), studies in humans link current cannabis use to lower plasma HIV RNA viral load (Milloy et al., 2015) and accelerated HIV DNA decay (Chaillon et al., 2020). In recent

HIV studies, including work from our group, current cannabis use has been associated with lower levels of peripheral and central inflammation (Castro et al., 2019; Manuzak et al., 2018; Rizzo et al., 2018; Watson et al., 2021), lower rates of global cognitive impairment, and better performance in verbal fluency and learning domains in adults with HIV (Watson et al., 2020). However, to our knowledge, no studies have examined the longitudinal impact of current cannabis use on global cognitive decline among older adults with HIV.

The current study sought to describe cannabis user profiles in later-life and examine benefits and risks of current cannabis use on cognitive and everyday function in a longitudinal cohort. First, we identified cannabis use patterns of older users and their demographic, clinical, and HIV disease correlates. In aim 1, we examined three levels of cannabis-cognition relationships: (1a) long-term effects of average cannabis use on overall global cognition and (1b) global cognitive declines; (1c) short-term effects of recent cannabis use on visit-specific cognitive performance. Average cannabis use was characterized by each participant's pattern of use over study follow-up (between-person effect) and recent cannabis use was characterized by use at each study visit (within-person effect). Given previously observed anti-inflammatory effects of cannabis in HIV, we hypothesized that average occasional cannabis use over study follow-up would relate to better cognitive function overall and less steep cognitive declines over time compared no cannabis use. For recent cannabis use, we hypothesized that some measures of heavy, recent use would relate to worse cognitive performance at specific visits. To aid interpretation of global findings, we also explored cognitive domain-specific outcomes. In aim 2, to determine the functional relevance of our findings, we examined the effects of recent and average cannabis use on everyday functioning difficulties and declines over study follow-up. Cognitive domain and functional analyses were exploratory.

Methods

Participants were 297 community-dwelling older adults with HIV who were followed longitudinally for 2–10 study visits with comprehensive assessments every 6–12 months for up to 10 years (average total visits = 3.4, average total years of follow up = 3.9, average years between visits = 1.1). All participants were enrolled in NIH-funded research studies at UC San Diego's HIV Neurobehavioral Research Program (HNRP). Study design and cohort selection have been described in detail previously (Heaton et al., 2011a). All study procedures were approved by the UC San Diego Institutional Review Board, and all participants provided written, informed consent. Longitudinal study visits took place from 2000 to 2020.

Inclusion criteria for the current study were availability of detailed cognitive, medical, and substance use data at all visits. Exclusion criteria for HNRP studies include diagnosis of a psychotic disorder or a neurological or medical condition that may significantly affect cognitive test results (e.g., schizophrenia, epilepsy). Exclusion criteria for the current analyses were (1) positive drug screening test for non-prescription, addictive substances other than cannabis; (2) report of any substance use disorder in the past year other than cannabis; (3) reported in the past year of cocaine, methamphetamine, amphetamine, other stimulants, heroin, other opioids, sedatives, hallucinogens, phencyclidine, ketamine, or inhalants.

Demographics. Demographic information (age, education, sex, race, ethnicity, employment) was collected by self-report. Reading level was assessed with the Wide Range Achievement Test (WRAT) (Wilkinson & Robertson, 2006).

Cannabis Use. Cannabis use was characterized at each study visit by self-report and THC-positive (THC+) urine toxicology which was determined by the presence of cannabis metabolites in urine. Frequency, quantity, and recency of cannabis use were captured via

timeline follow-back (TLFB) interview (Robinson, Sobell, Sobell, & Leo, 2014). Average cannabis use over study follow-up and recent cannabis use at each study visit were assessed to characterize long-term and short-term effects of cannabis on outcomes of interest. To define average cannabis use, frequency of cannabis use in the past six months was reported at each study visit and averaged across all visits to create a person-specific longitudinal average cannabis use score. Consistent with prior published longitudinal studies of cannabis use and cognition (McKetin et al., 2016), we next categorized cannabis users by greater or less than weekly use: frequent cannabis users (2–7 days per week) (n = 23) and occasional cannabis users (once weekly or less) (n = 83). To assess recent cannabis use, we examined days of cannabis use in the past month, estimated grams of cannabis used in the past month, and THC+ urine toxicology.

Cognition. Participants completed a standardized and validated battery of neuropsychological tests at each study visit, assessing global cognition and seven domains: verbal fluency, executive function, learning, memory/delayed recall, attention/working memory, processing speed, and motor skills (Carey et al. 2004). Raw neuropsychological test scores were converted to practice-effect corrected scaled scores (M = 10; SD = 3) and averaged across the entire battery and within cognitive domains to generate global and domain-specific scaled scores, which were used as cognitive trajectory outcome variables (Cysique et al., 2011). Scaled scores were not adjusted for demographics in order to allow for examination of the influence of age, sex, race/ethnicity, and education on cognitive change over time.

Everyday Function. Three measures of everyday function were assessed at each study visit, capturing functional status, experience of cognitive difficulties, and declines in independent functioning. Functional status was assessed by a certified neuromedical interviewer via the Karnofsky Scale of Performance, which has been validated in HIV (Gandhi et al., 2011), and

ranges from 0 (death) to 100 (unimpaired/normal functional status). Perceived cognitive difficulties in everyday life were assessed by the Patient's Assessment of Own Functioning Inventory (PAOFI), a 33-item self-report measure (Chelune, Heaton, & Lehman, 1986). PAOFI score represents the number of cognitive symptoms in daily life that participants endorsed experiencing "fairly often" or more, and are considered clinically significant. Declines in instrumental activities of daily living (IADLs) were assessed by a modified version of 1969 Lawton & Brody Scale, a self-report measure in which participants rate their current functioning relative to their previous highest level of functioning on 13 IADL domains (e.g., medication management, transportation, financial management, housekeeping) (Heaton et al., 2004). The total score is the number of IADL domains for which functional declines and a need for increased assistance are reported.

Clinical and HIV Disease. Participants completed a comprehensive neuromedical examination, including a structured, clinician-administered questionnaire and collection of blood and urine. Clinical factors assessed included psychiatric, medical, and substance use comorbidities. Current depressive symptoms were assessed by the Beck Depression Inventory (BDI-II) (Beck, Steer, & Brown, 1996). Diabetes, hypertension, and hyperlipidemia diagnoses were collected by self-report. Alcohol and tobacco use were assessed by TLFB interview and defined by use in the past month. HIV infection was confirmed by enzyme-linked immunosorbent assay with Western blot confirmation, and detailed ART use history was obtained by a standardized questionnaire. Duration of HIV disease was estimated by time since first positive HIV test. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, and CD4+ T cells (flow cytometry) assays were performed. Levels of HIV RNA in plasma were measured using reverse transcriptase-polymerase chain

reaction (Amplicor, Roche Diagnostics, Indianapolis, IN), with a lower limit of quantification (LLQ) of 50 copies/ml. HIV RNA concentration was dichotomized as detectable vs. undetectable at the LLQ.

Covariate Selection. For multi-level models examining cognitive outcomes, demographic, clinical, and HIV disease variables were selected for inclusion as covariates if they differed by cannabis use group at baseline at $p < 0.05$. Variables selected as covariates using this method were years of education, race/ethnicity, and estimated duration of HIV. Additional covariates were selected if they were associated with average overall global cognition across the study at $p < 0.05$. Variables selected as covariates using this method were age, years of education, race/ethnicity, diabetes, hypertension, and tobacco use. To adjust for historical and current HIV disease severity, we included nadir CD4+ T-cell count <200/μL and current CD4+ T-cell count <200/μL as covariates.

Statistical analyses. Group differences on baseline characteristics by cannabis use group were examined using analysis of variance or Wilcoxon tests for continuous variables and χ^2 tests for categorical variables. Pairwise comparisons were examined using Tukey's HSD or chi-square tests with Bonferroni adjustments. Cannabis use over study follow-up did not predict length of study follow-up ($p > .05$) so data were assumed to be missing at random.

Multi-level models examined: (1a) the long-term effects of average cannabis use on overall global cognition (scaled scores) and (1b) global cognitive declines (i.e., between-person effects); and (1c) the short-term effect of recent cannabis use on visit-specific global cognition (i.e., within-person effect). To accomplish this, we first examined a model that was unadjusted for covariates, and next we examined a model that was adjusted for age, sex, education, race/ethnicity, diabetes, hypertension, tobacco use, estimated duration of HIV, nadir CD4+ T-cell

count <200/µL, and current CD4+ T-cell count <200/µL. The effect of person-mean centered age was used as a time scale and modeled as a random slope, allowing us to examine average cannabis use as a between-person predictor of global cognitive trajectory for each participant. Between-person effects capture the association of average cannabis use (i.e., overall pattern of cannabis use across study-follow up) on overall cognition (i.e., average cognition over the total study follow up period) and cognitive decline, while within-person effects capture the effect of visit-to-visit variation in cannabis use within an individual and estimate the influence of recent, heavy cannabis use on cognition at a specific time-point. To first identify which metric of within-person cannabis use best predicted variability in global cognition from visit-to-visit, we ran three separate multi-level models each examining a measure of recent cannabis use: days of cannabis use in the past month, grams of cannabis used in the past month, and THC+ urine toxicology. Any recent cannabis use measure that was associated with global cognition was included in the study's primary multi-level model that simultaneously examined the effects of average and recent cannabis use on cognitive outcomes. Random intercepts were specified and unstandardized model estimates and 95% confidence intervals are reported. Multi-level models were repeated for each cognitive domain to explore domain-specific effects of any relationships observed on global cognition.

To investigate whether cannabis effects extend to everyday functioning, we first examined whether the three recent measures of cannabis use predicted visit-to-visit variability in measures of everyday function (functional status, cognitive difficulties, IADL declines), and separately, whether average patterns of cannabis use predicted overall levels of functional decline over study follow-up.

Results

The study cohort of 297 older adults with HIV had an average baseline age of 56.2 years (*range* = 50–84). 89% of participants were male, 72% were gay or bisexual, and 62% were White or European American, 19% were Black or African American, 15% were Latino or Hispanic, 1% were Asian American, and 3% were Other. Baseline demographic, clinical, and HIV disease characteristics by cannabis user group are shown in *Table 1*. Years of follow-up since baseline ranged from 0.5 to 10 years (M = 3.9; SD = 2.8).

Cannabis User Profiles. 35.7% of the cohort (n = 106) endorsed cannabis use at some point during study follow-up. 7.7% (n = 23) reported frequent cannabis use (>weekly use) and 28.0% (n = 83) reported occasional cannabis use (≤weekly use) on average over study follow-up. Baseline cannabis use characteristics of occasional and frequent users are compared in *Table 2*. At baseline, occasional cannabis users averaged 3.5 days of cannabis use in the past month, with median 0.1 grams per day of use. Frequent cannabis users averaged of 26.1 days of use in the past month, with median 0.5 grams per day of use. Occasional compared to frequent cannabis users differed significantly by all cannabis use characteristics examined in *Table 2* at baseline.

Occasional cannabis users had more years of education than non-cannabis users and frequent cannabis users (p = 0.001). Occasional and frequent cannabis users were more likely to be White than non-users (p = 0.02). Occasional cannabis users had longer duration of HIV than non-users (p = 0.03). All other demographic, clinical, and HIV disease characteristics were comparable across cannabis use groups (Table 1).

Short-term Effects of Recent Cannabis Use on Global Cognition. Days of cannabis use in the past month and grams of cannabis used in the past month were not associated with worse global cognitive performance at each study visit (ps > 0.05). THC+ urine toxicology was

associated with worse global cognitive performance (b = –0.33, 95% CI = [–0.59, –0.07], p = 0.01), indicating that at visits when a participant was THC+ they performed worse relative to visits when they were THC-negative.

Unadjusted Cannabis Effects on Global Cognition and Global Cognitive Decline. In a multi-level model unadjusted for covariates, at the between-person level, occasional cannabis use and frequent cannabis use were associated with better global cognition compared to the non-user group (occasional: b = 0.77, 95% CI = [0.27, 1.27], p = 0.003; frequent: b = 1.02, 95% CI = [0.14, 1.91], p = 0.02). Rates of global cognitive decline did not differ by cannabis use group (ps > 0.05). At the within-person level, the negative association between THC+ urine toxicology and visit-specific cognitive performance remained significant (b = –0.37, 95% CI = [–0.61, –0.13], p = 0.002).

Adjusted Cannabis Effects on Global Cognition and Global Cognitive Decline. Results of the multi-level model examining effects of average and recent cannabis use on global cognitive function and global cognitive decline adjusted for covariates are presented in *Table 3*. Covariates included age, sex, race/ethnicity, education, diabetes, hypertension, tobacco use, HIV disease duration, nadir CD4+ T-cell count <200/µL, and current CD4+ T-cell count <200/µL. At the between-person level, occasional cannabis use remained significantly associated with better global cognition compared to the non-user group (b = 0.50, 95% CI = [0.03, 0.96], p = 0.03), while after covariate adjustment, frequent cannabis use was no longer associated with better global cognition (p = 0.50) compared to non-users. The effect of cannabis use group on rates of global cognitive decline remained non-significant (ps > 0.05) (Figure 1). At the within-person level, the negative effect of THC+ urine toxicology remained significant; when participants

tested positive for THC, they performed worse cognitively (b = –0.27, 95% CI = [–0.52, –0.02], p = 0.03), compared to visits when they did not test positive for THC.

Adjusted Cannabis Effects on Cognitive Domains. Examination of cognitive domain-specific outcomes revealed at the between-person level, that the better average global cognitive performance observed among occasional cannabis users compared to non-users was primarily driven by the domain of attention/working memory (b = 0.82, 95% CI = [0.19, 1.44], p = 0.01), with trend-level associations observed for verbal fluency (b = 0.56, 95% CI = [–0.06, 1.17], p = 0.07) and learning (b = 0.56, 95% CI = [–0.08, 1.20] p = 0.09). At the within-person level, the short-term adverse effect of THC+ urine toxicology on global cognition at specific study visits was driven by the domain of memory/delayed recall (b = -0.70, 95% CI = [–1.23, –0.17], p = 0.009). Cannabis use group was not related to rates of decline in any of the seven cognitive domains (ps > 0.05).

Cannabis Effects on Everyday Function. Average patterns of occasional and frequent cannabis use did not predict overall levels of functional status, reported experience of cognitive difficulties, nor IADL declines across study follow-up (ps > 0.05). More days of cannabis use in the past month, however, was associated with greater self-reported cognitive difficulties on the PAOFI (b = 0.07, 95% CI = [0.01, 0.13], p = 0.01) compared to fewer days of cannabis use. Days of cannabis use in the past month was unrelated to functional status and IADL declines at each study visit (ps > 0.05). THC+ urine toxicology and grams of cannabis used in the past month were unrelated to visit-to-visit variability in the functional status, cognitive difficulties, and IADL declines (ps > 0.05).

Discussion

In a longitudinal, well-characterized cohort of older adults with HIV, we found that occasional cannabis use in later-life was associated with better overall global cognition compared to no cannabis use, a potentially important finding given this population's increased vulnerability to cognitive impairment. There was no evidence that cannabis use moderates rates of global cognitive decline over the course of six months to 10 years, suggesting that cannabis use within the ranges observed in this study, including greater than weekly use in older age, is not a risk factor for early decline in any cognitive domain. Short-term decrements in global cognitive performance were detected at visits when older adults had THC+ urine toxicology, but this effect did not extend to reports of functional problems. The putative beneficial effect of average occasional cannabis use across follow-up was driven by better attention, learning, and verbal fluency performance, while the deleterious short-term effect of recent THC exposure was driven by poor memory performance. Together, these results suggest a dynamic relationship between cannabis use and cognition, and domain-specific findings suggest differing mechanisms may underlie the short-term versus longer term cannabis effects observed. Functionally, greater frequency of recent cannabis use was linked to greater self-reported cognitive difficulties, but all other average and short-term cannabis use metrics showed no effect on overall level nor visit-to-visit variability in functional status, cognitive difficulties, or IADL declines.

The present study provides several novel contributions to the current sparse literature that examines cannabis use and cognitive function among older adults (Pocuca et al., 2020; Scott et al., 2019; Weinstein & Sznitman, 2020). Occasional and frequent cannabis users did not show higher burden of medical comorbidities such as diabetes or hypertension compared to non-users, nor did occasional or frequent cannabis users show worse historical or current HIV disease

outcomes with similar levels of current CD4+ T-cell counts, current ART use, and undetectable plasma HIV RNA. Overall, examination of demographic, clinical, and HIV disease variables showed that later-life cannabis use was not associated with poor health outcomes. However, neither occasional nor frequent cannabis user groups were characterized by high-dose daily use in this cohort, precluding the generalizability of our findings to older adults who have heavier cannabis consumption patterns.

The more acute finding that memory performance was worse on visits when participants had recently used THC is consistent with the notion that commonly observed cannabis-associated deficits in verbal memory (Broyd et al., 2016) are due to the short-term pharmacological effects of THC, and these deficits resolve after short periods of cannabis abstinence (Schreiner & Dunn, 2012; Tait et al., 2011). While worse performance appears to be restricted to periods of heavier THC use in our analyses, even a short-term decrement in memory functioning could lead to challenges in everyday functioning such as medication management. However, THC+ urine toxicology was unrelated to variability in functional outcomes, suggesting these memory decrements may not substantially impair everyday function. An alternative explanation is that our self-report and clinically-rated functioning measures may not be sensitive to subtle changes in functioning as they are proxies of impairment in real-world functioning and subject to reporter bias (Schmitter-Edgecombe, Parsey, & Cook, 2011). Performance-based and direct observation everyday functioning measures may be advantageous to employ in future studies of cannabis use to improve the ecological validity of everyday function assessment. Future research is also needed to determine whether the biphasic, age- and dose-dependent effects of THC on memory observed in animal studies (i.e., low dose THC administration improves memory function selectively in older mice, while high dose THC induces memory

impairment) translate to older human populations (Calabrese & Rubio-Casillas, 2018; Sarne et al., 2018). Such work will be critical for establishing cannabinoid-specific recommendations for older adult medical and recreational use to limit any possible negative cognitive outcomes due to use of THC. Our results also underscore the importance of delineating short-term vs. long-term effects of cannabis on various indicators of cognitive performance, including cognitive variability from visit-to-visit, overall performance over time, and cognitive declines.

The short-term negative association between THC and memory performance did not extend to overall cognitive performance across the study. In fact, a pattern of occasional cannabis use across the study (≤weekly use) was associated with better global cognitive performance compared to no cannabis use, above and beyond demographic, clinical, and HIV disease predictors of cognition and correlates of cannabis use. This relationship was driven by performance in attention, learning, and verbal fluency, highlighting cognitive domains that are commonly affected in HIV, and are clinically relevant in predicting everyday functioning outcomes (Heaton et al., 2004). However, in this cohort, occasional cannabis did not predict improved functional outcomes as assessed by interviewer-determined functional status, self-reported cognitive difficulties, or self-reported IADL declines. As noted above, our metrics of everyday function could lack sensitivity to detect cannabis effects.

Our study's finding that occasional cannabis use is consistently linked to better overall global cognition in older age advances prior cross-sectional studies in adults with HIV which have observed positive associations between past or current cannabis use and cognition (Crook et al., 2020; Kallianpur et al., 2020; Watson et al., 2020). Cross-sectionally, null effects (Chang et al., 2006; Chang et al., 2020; De Francesco et al., 2019) and adverse effects of cannabis are also observed, in particular on learning and memory performance, selectively among moderate-to-

heavy cannabis users (Thames et al., 2016) and those with more advanced symptomatic HIV disease (Cristiani et al., 2004), indicating that harmful effects may be contingent on specific high levels of use or more severe HIV disease.

The study's average cannabis use findings have several possible interpretations. First, occasional cannabis users may have started with better cognition function as they had on average 1.2 more years of formal education than non-cannabis users. While we adjusted for education in our analyses and reading level, a proxy for educational quality, did not differ by cannabis use group, residual confounding related to educational experiences or other unmeasured sociocultural factors could have influenced our analyses. Any protective relationship observed between cannabis use and cognitive function may be due to the direct effects of cannabis and cannabinoids on cognition (e.g. via mitigation of chronic neuroinflammation and neural injury that contribute to cognitive dysfunction), or indirect effects (e.g. via amelioration of clinical symptoms such as chronic pain or sleep disturbances which can interfere with daily cognitive functioning). Evidence for direct cannabis effects are supported by animal and human studies which show cannabinoids can disrupt and attenuate age-related neuroinflammation (Aso & Ferrer, 2014; Di Marzo et al., 2015), and HIV-associated pro-inflammatory processes that are associated with cognitive impairment (Henriquez, Bach, Matos-Fernandez, Crawford, & Kaminski, 2020; Rizzo et al., 2019; Watson et al., 2021). Further, normalized patterns of functional brain connectivity have been observed in HIV+ cannabis using adults (Hall, Lalee, Bell, Towe, & Meade, 2021) compared to HIV+ non-users, while findings from a structural neuroimaging study indicate that heavier quantities of cannabis use (grams used in the past month) of cannabis use are associated with smaller entorhinal cortex and fusiform gyrus volumes in HIV+ adults (Thames et al., 2017). Heavy cannabis consumption may disrupt

endocannabinoid system homeostasis (Rotter et al., 2013), and eclipse any possible neuroprotective effects that cannabis may show in inflammatory conditions. While many older adults and people with HIV report cannabis use to treat conditions such as insomnia, anxiety, and depression that can negatively impact cognitive function (Hazekamp et al., 2013; Woolridge et al., 2005), future mechanistic studies are necessary to explore to what degree clinical symptom reductions and/or neuroinflammatory and brain functional or connectivity changes mediate cannabis-cognition relationships.

Cannabis use was unrelated to rates of decline in global cognition in our cohort, suggesting that while cannabis use may positively influence overall cognitive level and/or contribute to maintained cognitive function, its effects do not extend to slowing the process of age-related cognitive decline. While similar analyses that investigate the potential of cannabis products to attenuate or accelerate cognitive declines in older adults with and without HIV are scarce (Scott et al., 2019), one large longitudinal study of men with and without HIV found current daily and monthly cannabis use was associated with declines in processing speed selectively among men with HIV (Okafor et al., 2019). The authors note the magnitude of the effect was small and not clinically meaningful. Our study's cognitive domain specific analyses were inconsistent with this prior study, revealing null results across all seven domains, including processing speed. Our lack of findings of cognitive slope may also be influenced by the younger age distribution of our older adult cohort, with a mean age of 58.8 across all study visits. Older cohorts with greater variability in rates of cognitive decline may increase statistical power to detect cannabis effects on cognitive slope.

Our study has notable strengths. Our analytic approach was comprehensive in examining both average between-person and short-term within-person cannabis effects on overall cognition,

cognitive declines, and visit-to-visit changes in cognitive performance. Further, we took a robust approach to covariate adjustment for demographic, clinical, and HIV disease predictors of cognition and correlates of cannabis use. Lastly, our cannabis use measures were defined both by self-report and THC urine toxicology, while previous population-based investigations of cannabis use and cognitive function in older adults and adults with HIV relied solely on retrospective self-report which is vulnerable to recall bias (van der Pol et al., 2013), and these previous studies could not examine THC-specific effects.

Our results should be interpreted in light of several limitations. While we employed robust statistical methods in a longitudinal cohort, we cannot infer causality based on the observational design of the study. We also cannot discount the possibility that unmeasured third variables underlie the relationships observed. Our study lacked an HIV-negative older adult comparison group, which would enable us to examine whether the cannabis-cognition relationships we observed are restricted to people with HIV or extend to older adults without HIV. Demographically, our older adult sample is overwhelming male (89%), and majority White (62%), and does not reflect the gender, ethnic, and racial diversity of the national population of people with HIV, which is 22% women and 70% people of color (Prevention, 2018). Future analyses with greater representation of women, and ethnic and racial minorities who are disproportionately affected by the HIV epidemic are needed. While we initially aimed to examine cannabis use in vulnerable older adults, and the age of participants ranged from 50–84 years at baseline, the majority of our available cohort may be more appropriately described as middle-aged to older adults. Thus, our findings may not generalize to older adults ages 65 and older, who may be more susceptible to adverse cannabis effects and comprise the fastest growing cannabis user group in the U.S. Lastly, we did not collect detailed information about older

adults' medical or recreational motivations for cannabis use, nor the doses and cannabinoid profiles of products used. Detailed characterization of cannabinoid content in future research is needed to investigate the potential divergent effects on cognition by dose and cannabinoid (e.g., high THC vs. high CBD vs. 1:1 THC+CBD, as well as less-studied cannabinoids).

To our knowledge, this study is the first to characterize longitudinal patterns of current cannabis use and global cognitive performance over an average of 3.9 years in a cohort of older adults with HIV. We found no evidence that cannabis use influences risk for cognitive nor functional decline. Our findings suggest a short-term cognitive risk of THC-based cannabis products on memory performance, but a possible long-term global cognitive benefit from occasional later-life cannabis use. Further mechanistic work is needed to probe this positive finding to inform whether cannabinoids show therapeutic potential in treating chronically elevated neuroinflammation and reducing downstream cognitive problems in people with HIV. As older adult cannabis use in the U.S. continues to climb, further investigations are needed in more diverse aging cohorts to clarify any potential therapeutic or harmful effects of specific cannabis products, and inform guidelines for safe and efficacious cannabis use.

Table 1. Baseline characteristics of older adults with HIV by cannabis use (n = 297)

Characteristic	No cannabis use n = 191	Occasional cannabis use n = 83	Frequent cannabis use n = 23	p value
Demographics				
Age (years)	56.4 (6.0)	56.7 (6.1)	53.8 (4.0)	ns
Education (years)	13.7 (3.0)	14.9 (2.3)	13.1 (2.6)	0.001
Sex (% men)	81.1%	91.6%	87.0%	ns
Race/ethnicity				0.02
White	56.5%	71.1%	78.3%	
Black	20.4%	15.7%	13.0%	
Latino	20.4%	6.0%	8.7%	
Asian	0.5%	1.2%	0%	
Other	2.1%	6.0%	0%	
Employed	30.5%	33.7%	34.8%	ns
Reading level (WRAT)	100.1 (15.1)	103.6 (14.6)	100.8 (11.9)	ns
Clinical				
Depression symptoms	9 (3–16)	7 (4–13)	12 (4–24)	ns
Diabetes	23.0%	14.6%	19.1%	ns
Hypertension	52.4%	43.9%	38.1%	ns
Hyperlipidemia	54.0%	50.0%	52.4%	ns
Hepatitis C Virus	23.0%	12.2%	14.3%	ns
Past month tobacco use[1]	13.1%	16.9%	20.0%	ns
Past month alcohol use[1]	18.3%	31.3%	34.8%	ns
HIV Disease				
AIDS Diagnosis	68.6%	66.3%	65.2%	ns
Duration of HIV (years)	15.9 (7.4)	18.6 (7.7)	17.5 (8.2)	0.03
Nadir CD4+ T-cell count	133 (33–270)	170 (46–294)	138 (24–362)	ns
Current CD4+ T-cell count	556 (386–748)	636 (461–823)	603 (297–956)	ns
ART status (% on)	91.5%	92.8%	87.0%	ns
HIV RNA in plasma (% undetectable)	90.5%	90.7%	90.0%	ns

Data are presented as Mean (SD), Median (IQR), or %
Abbreviations: ns = non-significant ($p \geq 0.05$); [1]Use in the past month

Table 2. Cannabis use characteristics of occasional and frequent use groups at baseline

Characteristic	Occasional cannabis use *n* = 83	Frequent cannabis use *n* = 23	*p*-value
Age of first use	19.4 (7.0)	13.6 (4.2)	<.001
Total days used[1]	3.5 (7.3)	26.1 (7.1)	<.001
Total grams used[1]	0.3 (0–0.5)	7.5 (3–15)	<.001
Median grams/day[1,2]	0.1 (0–0.2)	0.5 (0.2–0.5)	<.001
Days since last use	21 (4–98)	1 (0.9–2)	<.001
THC+ urine toxicology	21.3%	86.4%	<.001

Data are presented as Mean (SD) or Median (IQR)
[1]Over the past month; [2]Per day of cannabis use

Table 3. Effects of average and recent cannabis use on global cognition and global cognitive decline among older adults with HIV

	Estimate	SE	p-value
Between-person level (long-term effects of average use)			
Outcome: Average Global Cognition Scaled Score			
Occasional cannabis use (vs. no use)	0.50	0.24	**0.03**
Frequent cannabis use (vs. no use)	0.29	0.43	0.50
Average age	-0.08	0.02	**<.001**
Sex	-0.28	0.15	0.06
Education	0.14	0.04	**<.001**
Race/ethnicity	-0.44	0.11	**<.001**
Diabetes	0.02	0.26	0.93
Hypertension	-0.48	0.23	**0.04**
Tobacco Use	-0.54	0.35	0.12
Average HIV duration	0.003	0.01	0.80
Nadir CD4+ T-cell count < 200/μL	0.09	0.19	0.62
Outcome: Global Cognitive Decline			
Slope of global cognition (for non-users)	-0.04	0.02	**0.04**
Occasional cannabis use (vs. no use)	0.02	0.03	0.52
Frequent cannabis use (vs. no use)	0.03	0.08	0.71
Within-person level (short-term effects of recent use)			
Outcome: Visit-to-visit Change in Global Cognition			
THC+ urine toxicology	-0.27	0.13	**0.03**
Current CD4+ T-cell count < 200/μL	-0.09	0.20	0.66

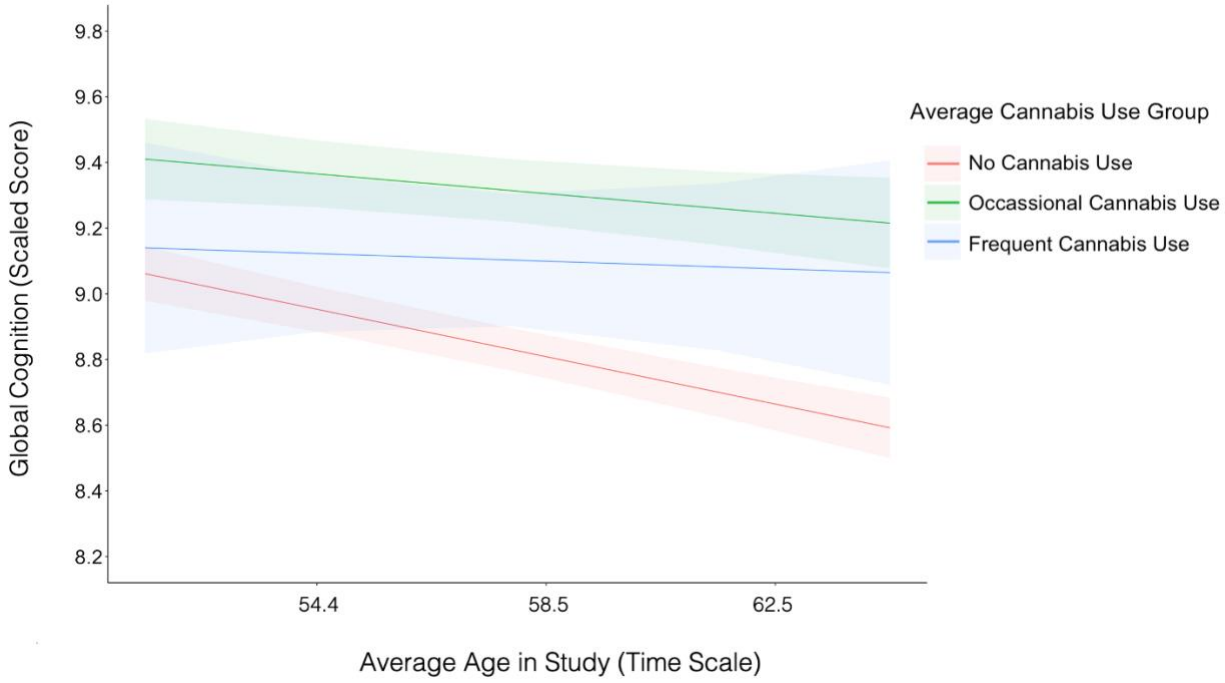

Figure 1. Occasional cannabis users demonstrated better global cognitive performance over time compared to non-users (b = 0.50, p = 0.03) among older adults with HIV. Frequent cannabis users and non-users did not differ in global cognitive performance (b = 0.29, p = 0.50), nor did occasional cannabis users and frequent cannabis users (b = 0.21, p = 0.65).

Rates of global cognitive decline did not differ between cannabis use groups (ps > 0.05) with similar trajectories of global cognitive decline between occasional cannabis users and non-users (b = 0.02, p = 0.52), frequent cannabis users and non-users (b = 0.03, p = 0.71), and occasional users and frequent users (b = 0.009, p = 0.91).

Notes: Intercepts, slopes, and 95% CI bands were derived from multi-level model estimates.

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DISCUSSION

This staple dissertation aimed to evaluate the effects of cannabis use on peripheral and central inflammation, neurocognitive performance, and everyday function in PWH and older adults. An overarching translational research goal of this project was to determine whether preclinical findings that demonstrate cannabinoids' anti-inflammatory and immune stabilizing actions extend to CNS outcomes in humans living with pro-inflammatory medical conditions. Three separate studies were designed to characterize different levels of cannabis exposure, investigate their independent influence on clinically-relevant outcomes, and probe potential inflammation-attenuating mechanisms. As cannabis use increases among PWH and older adults, this research is critical to identify risks and benefits of use, highlight cannabis-level and individual-level factors that may moderate cannabis' impacts, and aid in establishing parameters for safe and efficacious medical cannabis use in vulnerable populations. A final goal of these studies was to inform the future development of cannabinoid-based therapeutics, as currently there are no treatments available to address HIV-associated chronic neuroinflammation or downstream neurocognitive dysfunction in aging PWH.

In the Study 1 (N = 952), we examined rates of NCI across four groups categorized by current and past cannabis exposure and HIV status. PWH with past year cannabis use and a history of cannabis use disorder had lower rates of NCI and better performance in learning and verbal fluency domains compared to PWH with no cannabis use, while cannabis use was unrelated to rates of NCI among HIV-negative people. We did not find that the magnitude of the association between cannabis exposure and NCI was greater among older PWH, but there were a limited number of older adults with cannabis exposure in the cohort. Results suggested that the novel positive associations between cannabis use and neurocognitive function were specific to

PWH, which we speculated was due to the anti-inflammatory effects of cannabis buffering against pathological neuroinflammation in HIV.

In Study 2 (N = 234), we investigated this theory by examining levels of six pro-inflammatory biomarkers in CSF and plasma across groups defined by specific frequencies of cannabis use, given recent systemic anti-inflammatory findings observed selectively in daily cannabis users (Manuzak et al., 2018). Participants were categorized into daily cannabis using, moderate cannabis using (on average weekly use), and non-cannabis using PWH, and an HIV-negative non-cannabis using control group. 100% of daily cannabis users had THC+ urine toxicology at study visit, compared to 48% of moderate cannabis users. We found lower levels of CCL2/MCP-1 and CLCX10/IP-10 in CSF among daily cannabis using compared to non-cannabis using PWH. The lower levels of CCL2/MCP-1 and CLCX10/IP-10 observed in daily cannabis using PWH were similar to the HIV-negative non-cannabis using control group, suggesting that frequent cannabis exposure may reduce neuroinflammation in PWH to levels comparable to HIV-negative people. Plasma inflammatory biomarkers did not differ by cannabis use, suggesting cannabis modulates chemokine levels selectively in the CNS where elevated CCL2/MCP-1 and CLCX10/IP-10 promote neurotoxicity via activation and proliferation of microglia and chemotaxis of blood monocytes, but not in the periphery. We speculated that distinct effects in CSF vs. plasma could be due to (1) cannabinoids' lipid solubility, leading to amplified and prolonged effects in CSF compared to blood or (2) in PWH, much higher levels of CCL2/MCP-1 and CLCX10/IP-10 are typically observed in CSF compared to blood, which may have increased our ability to detect cannabis-related modulatory effects. Cognitive domain analyses revealed that lower CSF CCL2/MCP-1 and lower CSF CLCX10/IP-10 were associated

with better learning performance, in alignment with one cognitive domain finding from Study 1, but not with better verbal fluency performance.

In Study 3 (N = 297), we investigated the long- and short-term effects of cannabis use on global neurocognition, global neurocognitive declines, and functional declines, specifically in older adults with HIV, given the limited age range to detect age-specific cannabis-cognition relationships in Study 1. In a longitudinal cohort, an average pattern of occasional cannabis use (≤weekly) was associated with better overall global neurocognition compared to no cannabis use which was driven by attention/working memory, learning, and verbal fluency performances, revealing a roughly similar pattern to Study 1. THC-positive urine toxicology was linked to short-term decrements in memory performance compared to visits when older adults were THC-negative. Results suggest that neurocognitive deficits associated with THC-based products are temporary and do not extend to functional challenges in everyday life. Rates of neurocognitive decline did not differ by cannabis use, suggesting that the positive association between occasional cannabis use and overall neurocognitive level does not extend to slowing the process of age-related neurocognitive decline. Thus, if cannabis does exert any neuroprotective effects in older PWH, there is no signal from this cohort to suggest cannabinoid exposure mitigates age-related brain changes that drive steeper cognitive trajectories in late-life.

Taken together, results illustrate the dynamic and contingent influence of cannabis and cannabinoids on CNS function, and highlight positive, null, and negative cannabis effects on neurocognitive outcomes. Collectively, Studies 1 and 3 appear to affirm a positive relationship between cannabis use and global cognitive level in both mid-life and older adults with HIV, and cognitive domain findings show some consistency across the studies with higher learning and verbal fluency domains identified with current cannabis use in both Studies 1 and 3; while in

Study 2, lower neuroinflammation was linked selectively to better learning performance. In the general population, heavy cannabis exposure is frequently associated with worse verbal learning and memory (Broyd et al., 2016), and our findings point to distinct relationship in mid-life and older PWH who on average report occasional or frequent-to-daily cannabis use, but not high-dose cannabis use. Future investigations that integrate neuroimaging data are necessary to determine whether neuroprotective cannabinoid actions in PWH have some preference for the medial temporal and prefrontal neural circuitry that subserve verbal fluency and learning.

Cannabinoid-specific findings across the three studies may appear conflicting. In Study 2 among adult PWH, lower neuroinflammation was observed selectively among daily users who were THC-positive at study visit, while in Study 3, THC-positive urine toxicology predicted worse global and memory performance among older PWH compared to visits when an individual was THC-negative. Animal studies show THC has dose- and age-dependent effects which may partially explain discrepant findings across CNS outcomes of interest (Bilkei-Gorzo et al., 2017; Calabrese & Rubio-Casillas, 2018), and we were unable to examine low vs. high THC dose effects with our dichotomous urine toxicology measure. Given Study 2 findings' alignment with similar THC-specific analyses in chronic HIV-associated inflammation (Manuzak et al., 2018; Rizzo et al., 2019), we hypothesize that a certain level of THC exposure may be necessary to demonstrate inflammation-dampening effects in PWH. On the other hand, among older adults in HIV, there may be a threshold of THC exposure over which temporary difficulties in memory performance emerge. Given this negative association was specific to visit-to-visit variability in neurocognitive performance and did not result in self-reported functional changes, it will be important to clarify the temporal duration of any worse THC-driven memory performance and whether it predicts any negative clinical or everyday functioning outcomes for aging populations.

Future investigations which employ continuous measures of THC level such as direct measurement of THC metabolites in plasma may assist in detecting ranges and thresholds of beneficial vs. harmful THC exposure on inflammatory and neurocognitive outcomes. Furthermore, none of these studies examine other components of the cannabis plant beyond phytocannabinoid THC; thus, we cannot rule out the possibility that other cannabinoids (e.g., CBD, CBG, CBC, CBN, etc.) or specific combinations of other cannabinoids with THC are necessary to drive inflammation-reducing effects.

All three studies examined cross-sectional relationships between different levels of cannabis use and demographic, clinical, and HIV disease characteristics, and broadly showed that among PWH including among older PWH, occasional, moderate, and frequent-to-daily cannabis use were not related to worse HIV disease characteristics such as lower rates of ART use or higher likelihood of detectable HIV RNA, nor higher rates of medical and psychiatric comorbidities. Some exceptions to this include in Study 1, past major depressive disorder was higher among cannabis-using PWH compared to non-cannabis-using PWH, while rates of current major depressive disorder were similar. In Study 1, rates of past substance use disorder for alcohol, cocaine, methamphetamine, and sedatives were higher also among cannabis using compared to non-cannabis using PWH. Overall, our HIV+ cohorts endorsed a range of cannabis use intake patterns, but even among the daily users (Study 2; $n = 31$) and frequent users (>weekly) (Study 3; $n = 23$), median daily consumption endorsed was not heavy (Study 2 and Study 3; 0.5 grams per day of use), which may in part reflect patterns of use for medical motivations. Our study findings on neuroinflammation, neurocognition, and everyday function should remain contextualized to these cannabis user profiles and the context of HIV disease, and cannot be simply generalized to other populations of cannabis users or disease contexts.

Overall limitations

Several limitations of these dissertation studies should be noted. First, all three studies are observational retrospective cohorts which were not originally designed to study the influence of cannabis use on cognitive, functional, and inflammatory outcomes. Causality from observed associations cannot be directly inferred from cross-sectional (Study 1, Study 2) nor longitudinal (Study 3) observational analyses. Second, all three studies lacked detailed information about cannabis use such as specific dosing and timing, route of exposure (smoking, vaping, edibles), qualitative information about motivations for and cultural context of use, and cannabinoid content of products used. Further, we used retrospective self-report to characterize cannabis user groups, which is prone to inaccurate estimation (van der Pol et al., 2013). While Studies 2 and 3 included measurement of THC urine toxicology which allowed us to define cannabis use groups by exposure to a specific cannabinoid, this dichotomous variable did not allow us to determine level of THC exposure. Third, while Study 1 included an HIV-negative cannabis-using group (n = 44), Studies 2 and 3 lacked such balanced design due to sample size limitations of HIV-negative individuals in available cohorts. Critical questions remain as to whether the associations between cannabis use and reduced CNS inflammation observed in Study 2 or better long-term global neurocognition observed in Study 3 extend to cannabis-using HIV-negative individuals, and in particular HIV-negative older adults. Cannabis use is expanding faster in older adults than any other age group in the U.S., and scant research examines its neurocognitive effects (Pocuca et al., 2020).

Overall implications

The vast majority of the current literature on cannabis-cognition relationships focus on chronic, heavy use and adolescent and young adult cohorts. These three dissertation studies

conjointly contribute to addressing a major research gap examining cannabis use and neurocognitive function among individuals living with chronic, pro-inflammatory disease and older adults. These populations increasingly use cannabis products, may benefit from cannabinoids' therapeutic properties, and are at risk for cognitive and functional decline. Together, these studies employed cross-sectional and longitudinal analyses of cannabis use to demonstrate cannabis effects vary by cognitive domain, disease context, patterns of cannabis use frequency, and cannabinoid content. Specifically, current cannabis use is linked to lower neurocognitive impairment selectively in PWH and not among HIV-negative adults, a moderate daily dose of THC may modulate pro-inflammatory chemokine response in the CNS in PWH, and among older PWH, weekly or less cannabis use may enhance overall global cognitive functioning, while recent use of THC may temporarily worsen memory performance. Findings highlight that further examination of the risk-benefit ratio of cannabis use in late-life is critical with active consideration of moderating factors.

Our results lay the groundwork for future mechanistic studies to characterize direct or indirect pathways through which cannabinoids may improve or maintain cognitive functioning that is relevant to everyday life (i.e. via mitigation of neurotoxicity that contributes to cognitive dysfunction or via amelioration of clinical symptoms such as chronic pain and sleep disturbances which can interfere with cognitive performance). Clinically, our work can inform guidelines for safe and efficacious medical cannabis use and development of cannabinoid therapeutics that aid in reducing persistent neuroinflammation and downstream neurocognitive impairment. In the future, specific cannabinoid doses and combinations may be identified that exert therapeutic effects on common clinical symptoms and stabilize cognitive functioning for PWH and older adults, improving their quality of life.

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