UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Using Ecological Momentary Assessment to Improve Assessment of Self-Reported Cognitive Difficulties among Adults with Comorbid HIV and Heavy Alcohol Use

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

in

Clinical Psychology

by

Emily Waller Paolillo

Committee in charge:

University of California San Diego

Professor David J. Moore, Chair
Professor Robert K. Heaton
Professor Raeanne C. Moore

San Diego State University

Professor Paul E. Gilbert
Professor Scott Roesch

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The dissertation of Emily Waller Paolillo is approved, and it is acceptable in quality and form for publication on microfilm and electronically.

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University of California San Diego

San Diego State University

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VITA

EDUCATION

2015-2021 **Doctor of Philosophy** in Clinical Psychology (Major Area of Study: Neuropsychology)
San Diego State University/UC San Diego Joint Doctoral Program in Clinical Psychology (APA-accredited)

2015-2017 **Master of Science** in Clinical Psychology
San Diego State University

2010-2014 **Bachelor of Science** in Psychology (Minor: Neuroscience)
City University of New York (CUNY) Macaulay Honors College at Brooklyn College
Summa Cum Laude

ACADEMIC HONORS, AWARDS, & SCHOLARSHIPS

2020-2021 Philanthropic Educational Organization (P.E.O.) Scholar Award
2019 Ted Blau Student Poster Award, National Academy of Neuropsychology (NAN)
2019 Gerald Rosenbaum Neuropsychology Dissertation Research Award, UC San Diego
2018-2020 F31 Predoctoral Fellowship, Ruth L. Kirschstein Individual National Research Service Award (NRSA), National Institute on Alcohol Abuse and Alcoholism (NIAAA): "Using Ecological Momentary Assessment to Improve Self-Reported Cognitive Functioning among Adults with Comorbid HIV/AIDS and Heavy Alcohol Use" (F31 AA027198). PI: Emily W. Paolillo (Primary Sponsor: David J. Moore, Ph.D.)
2018-2019 UC San Diego Chancellor's Research Excellence Scholarship Grant Award, "Heavy Drinking and Antiretroviral Adherence Don't Mix: Assessing Real-Time Relationships Using Ecological Momentary Assessment and Wearable Alcohol Biosensors" (Primary Mentor: David J. Moore, Ph.D.)
2018-2019 University Graduate Fellowship, San Diego State University [awarded, but declined due to inability to take concurrent awards]
2017-2018 HIV Neurobehavioral Research Center (HNRC) Developmental Grant Award, "Improving Self-Report of Cognitive and Everyday Functioning among People Living with HIV/AIDS" (Primary Mentor: David J. Moore, Ph.D.)
2015-2017 T32 Predoctoral Fellowship, Ruth L. Kirschstein Institutional NRSA, NIAAA: "Alcohol Research in the Science/Practitioner Model" (T32 AA013525). PI: Edward P. Riley, Ph.D.
2013 Undergraduate Research Fellowship, Neuroscience Research Experience for Undergraduates at Brooklyn College, National Science Foundation: Award #1156870
2010-2014 CUNY Macaulay Honors Scholarship, Full Tuition
2010-2014 Dean's List, CUNY Brooklyn College

PEER-REVIEWED PUBLICATIONS

1. **Paolillo, E. W.**, Saloner, R., Kohli, M., Watson, C. W-M., Moore, R. C., Heaton, R. K. & Moore, D. J. (In Press). Binge drinking relates to worse neurocognitive functioning among adults aging with HIV. *Journal of the International Neuropsychological Society*.
2. Sun-Suslow, N., Campbell, L. M., Tang, B., Fisher, A., Lee, E., **Paolillo, E. W.**, Heaton, A., & Moore, R. C. (In Press). Use of Digital Health technologies to examine subjective and objective sleep with next-day cognition and daily indicators of health in persons with and without HIV. *Journal of Behavioral Medicine.*
3. Herbert, M. S., Woolridge, J. S., **Paolillo, E. W.**, Depp, C. A, & Moore, R. C. (2021). Social contact frequency and pain among older adults with HIV: An ecological momentary assessment study. *Annals of Behavioral Medicine*.
4. Saloner, R., **Paolillo, E. W.**, Heaton, R. K., Grelotti, D. J., Stein, M.B., Miller, A. H., Atkinson, J. H., Letendre, S. L., Ellis, R. J., Grant, I., Iudicello, J. E., & Moore, D. J. (2021). Chronically elevated depressive symptoms interact with acute increases in inflammation to predict worse neurocognition among people with HIV. *Journal of NeuroVirology, 27*(1), 160-167.
5. Moore, R. C., **Paolillo, E. W.**, Sundermann, E. E., Campbell, L. M., Delgadillo, J., Heaton, A., Swendsen, J., Depp, C. A. (2021). Validation of the mobile verbal learning test: Illustration of its use for age and disease-related cognitive deficits. *International Journal of Methods in Psychiatric Research, 30*(1)*, e1859.*
6. Kamalyan, L., Yang, J-A, Pope, C., **Paolillo, E. W.**, Campbell, L. M., Tang, B., Marquine, M. J., Depp, C. A., & Moore, R. C. (2020). Increased Social Interactions Reduce the Association between Constricted Life-Space and Lower Daily Happiness in Older Adults with and without HIV: A GPS and Ecological Momentary Assessment Study. *American Journal of Geriatric Psychiatry*. doi: 10.1016/j.jagp.2020.11.005.
7. Campbell, L. C., **Paolillo, E. W.**, Heaton, A., Tang, B., Depp, C. A., Granholm, E., Heaton, R. K., Swendsen, J., Moore, D. J., & Moore, R. C. (2020). Daily Activities Related to Mobile Cognitive Performance in Middle-Aged and Older Adults: An Ecological Momentary Cognitive Assessment Study. *JMIR Mental Health*. doi: 10.2196/19579. PMID: 32969829.
8. Saloner, R., Cherner, M., Grelotti, D. J., **Paolillo, E. W.**, Moore, D. J., Heaton, R. K., Letendre, S. L., Kumar, A., Grant, I., & Ellis, R. J. (2020). Lower CSF homovanillic acid relates to higher burden of neuroinflammation and depression in people with HIV disease. *Brain Behavior and Immunity, 90*, 353-363. doi: 10.1016/j.bbi.2020.09.012. PMID: 32966871.
9. Kohli, M., **Paolillo, E. W.**, Saloner, R., Umlauf, A., Ellis, R. J., & Moore, D. J. (2020). The effects of low-risk drinking on neurocognition among older persons living with HIV as compared to those without HIV. *Alcoholism: Clinical and Experimental Research.* doi: 10.1111/acer.14379. PMID: 32449941.
10. Campbell, L. M., **Paolillo, E. W.**, Bryan, R., Marquie-Beck, J., Moore, D. J., Nebeker, C., & Moore, R. C. (2020). Informing Informed Consent for HIV Research. *Journal of*

Empirical Research on Human Research Ethics. doi: 10.1177/1556264620933766. PMID: 32560591.

11. Sun-Suslow, N., **Paolillo, E. W.**, Morgan, E. E., Letendre, S., Iudicello, J., & Moore, D. J. (2020). Frailty and HIV disease synergistically increase risk of HIV-associated Neurocognitive Disorders. *Journal of Acquired Immune Deficiency Syndromes, 84*(5), 522-526. doi: 10.1097/QAI.0000000000002391. PMID: 32345795.

12. **Paolillo, E. W.**, Pasipanodya, E. C., Moore, R. C., Pence, B. W., Atkinson, J. H., Grelotti, D. J., Grant, I., Heaton, R. K., & Moore, D. J. (2020). Cumulative burden of depression and neurocognitive decline among persons with HIV: A longitudinal study. *Journal of Acquired Immune Deficiency Syndromes, 84*(3), 304-312. doi: 10.1097/QAI.0000000000002346. PMID: 32195746.

13. Moore, R. C., Campbell, L. M., Delgadillo, J. D., **Paolillo, E. W.**, Sundermann, E. E., Holden, J., Schweitzer, P., Heaton, R. K., & Swendson, J. (2020). Smartphone-based measurement of executive function in older adults with and without HIV. *Archives of Clinical Neuropsychology, acz084.* doi: 10.1093/arclin/acz084. PMID: 31942632.

14. Saloner, R., **Paolillo, E. W.**, Kohli, M., Moore, D. J., Grant, I., & Cherner, M. (2020). Genetic variation in alcohol dehydrogenase is associated with neurocognition in men with HIV and history of alcohol use disorder: Preliminary findings. *Journal of NeuroVirology, Epub.* doi: 10.1007/s13365-019-00825-z. PMID: 31933193.

15. 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*, 56-64. doi: 10.1097/QAI.0000000000002211. PMID: 31809361.

16. **Paolillo, E. W.**, Sun-Suslow, N., Pasipanodya, E. C., Morgan, E. E., Ellis, R. J., Jeste, D. V. & Moore, D. J. (2020). Pre-frailty predicts cognitive decline at two-year follow-up in persons living with HIV. *Journal of NeuroVirology, 26,* 168-180. doi: 10.1007/s13365-019-00814-2. PMID: 31858484.

17. Pasipanodya, E. C., Montoya, J. L., Campbell, L. M., Hussein, M. A., Saloner, R., **Paolillo, E. W.**, Jeste, D. V., Letendre, S. L., McCutchan, J. A., Heaton, R. K., & Moore, D. J. (2019). Metabolic risk factors as differential predictors of profiles of cognitive impairment among older HIV+ and HIV- adults. *Archives of Clinical Neuropsychology, Epub*. doi: 10.1093/arclin/acz040. PMID: 31696212

18. **Paolillo, E. W.**, Saloner, R., Montoya, J. L., Campbell, L. M., Pasipanodya, E. C., Iudicello, J., Moore, R. C., Letendre, S. L., Jeste, D. V., & Moore, D. J. (2019). Frailty in comorbid HIV and lifetime methamphetamine use disorder: Associations with neurocognitive and everyday functioning. *AIDS Research and Human Retroviruses*, *Epub*. doi: 10.1089/AID.2019.0062. PMID: 31303012.

19. Saloner, R., **Paolillo, E. W.**, Umlauf, A., Moore, D. J., Heaton, R. K., Grant, I., Cherner, M., & the TMARC Group (2019). Conditional effects of lifetime alcohol consumption on methamphetamine associated neurocognitive performance. *Journal of the International Neuropsychological Society, Epub,* 1-13. doi: 10.1017/S1355617719000493. PMID: 31179969. PMCID: PMC6733657.

20. Rooney, A. S., Moore, R. C., **Paolillo, E. W.**, Gouaux, B., Umlauf, A., Letendre, S. L., Jeste, D. V., Moore, D. J., & the HIV Neurobehavioral Research Program (2019). Depression and aging with HIV: Associations with health-related quality of life and positive psychological factors. *Journal of Affective Disorders, 251,* 1-7. doi: 10.1016/j.jad.2019.03.025. PMID: 30884371. PMCID: PMC6705595.

21. Saloner, R., Campbell L., Serrano, V., Montoya, J. L., Pasipanodya, E., **Paolillo, E. W.**, Franklin, D., Heaton, R. K., Moore, D. J., & the HNRP Group (2019). Neurocognitive SuperAging in older adults living with HIV: Demographic, neuromedical and everyday functioning correlates. *Journal of the International Neuropsychological Society, 25,* 507-519. doi: 10.1017/S1355617719000018. PMID: 30890191. PMCID: PMC6705613.

22. **Paolillo, E. W.**, Inkelis, S. M., Heaton, A., Saloner, R. Moore, R. C., & Moore, D. J. (2019). Age of last alcohol use disorder relates to processing speed among older adults living with HIV. *Alcohol and Alcoholism, 54,* 139-147. doi: 10.1093/alcalc/agz008. PMID: 30796775. PMCID: PMC6476412.

23. Montoya, J. L., Campbell, L. M., **Paolillo, E. W.**, Ellis, R. J., Letendre, S. L., Jeste, D. L., & Moore, D. J. (2019). Inflammation relates to poorer complex motor performance among adults living with HIV on suppressive antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes, 80*, 15-23. doi: 10.1097/QAI.0000000000001881. PMID: 30365450. PMCID: PMC6289807.

24. Sundermann, E. E., Heaton, R. K., Pasipanodya, E., Moore, R. C., **Paolillo, E. W.**, Rubin, L. H., Moore, D. J., & the HNRP Group. (2018). Sex differences in HIV-associated cognitive impairment. *AIDS, 32*, 2719-2726. doi: 10.1097/QAD.0000000000002012. PMID: 30407251. PMCID: PMC6396274.

25. **Paolillo, E. W.**, Obermeit, L. C., Tang, B., Depp, C. A., Vaida, F., Moore, D. J., & Moore, R. C. (2018). Smartphone-based ecological momentary assessment (EMA) of alcohol and cannabis use in older adults with and without HIV infection. *Addictive Behaviors, 83,* 102-108. doi: 10.1016/j.addbeh.2017.10.016. PMID:29126667. PMCID: PMC5920804.

26. Oppenheim, H., **Paolillo, E. W.**, Moore, R. C., Ellis, R., Grant, I., & Moore, D. J. (2018). Neurocognitive functioning predicts frailty index in HIV. *Neurology, 91,* e162-e170. doi: 10.1212/WNL.0000000000005761. PMID: 29875216. PMCID: PMC6053109.

27. **Paolillo, E. W.**, Tang, B., Depp, C. A., Rooney, A. S., Vaida, F., Kaufmann, C. N., Mausbach, B. T., Moore, D. J., & Moore, R. C. (2018). Temporal associations between social activity and mood, pain, and fatigue in older adults with HIV: An ecological momentary assessment study. *JMIR Mental Health, 5,* e38. doi: 10.2196/mental.9802. PMID: 29759960. PMCID: PMC5972192.

28. **Paolillo, E. W.**, McKenna, B. S., Nowinski, C. J., Thomas, M. L., Malcarne, V. L., & Heaton, R. K. (2018). NIH Toolbox® emotion batteries for children: Factor-based composites and norms. *Assessment, 1073191118766396 [Epub ahead of print]*. doi: 10.1177/1073191118766396. PMID: 29618218. PMCID: PMC6205918.

29. Fazeli, P. L., Casaletto, K., **Paolillo, E.**, Moore, R. C., & Moore, D. J. (2017). Screening for neurocognitive impairment in HIV-positive adults aged 50 and older: Montreal Cognitive Assessment relates to self-reported and clinician rated functional ability. *Journal of*

Clinical and Experimental Neuropsychology, 39, 842-853. doi: 10.1080/13803395.2016.1273319. PMID: 28122474. PMCID: PMC5542876.

30. Moore, R. C., **Paolillo, E. W.**, Heaton, A., Fazeli, P. L., Jeste, D. V., & Moore, D. J. *(*2017). Clinical utility of the UCSD Performance-Based Skills Assessment – Brief (UPSA-B) in adults living with HIV: Associations with neuropsychological impairment and patient-reported everyday functioning difficulties. *PLoS ONE, 12,* e0183614. doi: 10.1371/journal.pone.0183614. PMID: 28837678. PMCID: PMC5570272.

31. **Paolillo, E. W.**, Gongvatana, A., Umlauf, A., Letendre, S. L. & Moore, D. J. (2017). At-risk alcohol use is associated with antiretroviral therapy non-adherence in adults living with HIV/AIDS. *Alcoholism: Clinical and Experimental Research, 41*, 1518-1525. doi: 10.1111/acer.13433. PMID: 28679147. PMCID: PMC5564671.

32. Rabin, L. A., **Paolillo, E.**, & Barr, W. B. (2016). Stability in test-usage practices of clinical neuropsychologists in the United States and Canada over a 10-year period: A follow-up survey of INS and NAN members. *Archives of Clinical Neuropsychology, 31*, 206-230. doi: 10.1093/arclin/acw007. PMID: 26984127.

PROFESSIONAL PRESENTATIONS

1. **Paolillo, E. W.**, Saloner, R., Watson, C. W-M., Ellis, R. J., Letendre, S. L., 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 session presentation at the 49th annual meeting of the International Neuropsychological Society, San Diego, CA.

2. Sun-Suslow, N., **Paolillo, E. W.**, Saloner, R., Letendre, S. L., Morgan, E. E., & Moore, D. J. (2021, February). *Frailty and cognition: Cross-sectional comparison of the Fried Phenotype, Rockwood Frailty Index, and Veterans Aging Cohort (VACS) Index on HIV-associated neurocognitive disorders.* Poster session to be presented at the 49th annual meeting of the International Neuropsychological Society, San Diego, CA.

3. 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 session presentation at the 49th annual meeting International Neuropsychological Society, San Diego, CA.

4. Saloner, R., Lobo, J., **Paolillo, E. W.**, Letendre, S. L., Cherner, M., Grant, I., Heaton, R. K., Ellis, R. J., & Moore, D. J. (2021, February). *Cognitive and physiologic reserve uniquely contribute to superior neurocognitive abilities in adults aging with HIV*. Poster session to be presented at the 49th annual meeting of the International Neuropsychological Society, San Diego, CA.

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

6. Kohli, M., Sun-Suslow, N., **Paolillo, E. W.**, Gasemaltayeb, R., Tang, B., Jeste, D. V., Ellis, R., Moore, R. C., & Moore, D. J. (2020, February). *Slower Gait Speed is Differentially Associated with Worse Neurocognition among Persons with and without HIV*. Poster session presented at the 48th annual meeting of the International Neuropsychological Society, Denver, CO.

7. Parrish, E. M., **Paolillo, E. W.**, Filip, T. F., Kamarsu, S., Quynh, A., Eyler, L. T., Depp, C. A., & Moore, R. C. (2020, February). *Relationships between daily mood states and real-time cognitive performance in individuals with bipolar disorder and healthy comparators*. Poster session presented at the 48th annual meeting of the International Neuropsychological Society, Denver, CO.

8. Sun-Suslow, N., **Paolillo, E. W.**, Morgan, E. E., Letendre, S. L., & Moore, D. J. (2020, February). *The moderating effect of frailty syndrome on the relationship between HIV disease severity and HIV-associated neurocognitive disorders*. Paper session presentation at the 48th annual meeting of the International Neuropsychological Society, Denver, CO.

9. 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 TNF-alpha in CSF among people living with HIV*. Poster session presented at the at 48th annual *meeting* of the International Neuropsychological Society, Denver, CO.

10. **Paolillo, E. W.**, Hussain, M. A., Moore, R. C., Moore, D. J., & Heaton, R. K. (2019, November). *Engagement in cognitively demanding activities is associated with neurocognitive test performance and perceived cognitive difficulties among adults with and without HIV*. Poster session presented at the 39th annual meeting of the National Academy of Neuropsychology, San Diego, CA.

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

12. **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 session presented at the 10th International Workshop on HIV & Aging, New York, NY.

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

14. **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 session presented at the 42nd annual meeting of the Research Society on Alcoholism, Minneapolis, MN.

15. Kohli, M., **Paolillo, E. W.**, Saloner, R., Umlauf, A., Ellis, R. J., & Moore, D. J. (2019, June). *The effects of light-moderate drinking on cognition among persons living with HIV as*

compared to those without HIV. Poster session presented at the 42nd annual meeting of the Research Society on Alcoholism, Minneapolis, MN.

16. Saloner, R., **Paolillo, E. W.**, Kohli, M., Moore, D. J., Grant, I., & Cherner, M. (2019, June). *Alcohol dehydrogenase 4 genetic polymorphism (rs1126671) is associated with executive function and working memory in men with HIV and history of alcohol use disorder*. Poster session presented at the 42nd annual meeting of the Research Society on Alcoholism, Minneapolis, MN.

17. Montoya, J. L., **Paolillo, E. W.**, Hussain, M. A., Moore, A., Moore, D. J., Moore, R. C. (2019, March). *Concurrent association between substance use and social activity among older adults living with HIV*. Poster session presented at the 40th annual meeting of the Society of Behavioral Medicine, Washington, D.C.

18. **Paolillo, E. W.**, Pasipanodya, E.C., Montoya, J. L., Moore, R. C., Heaton, R. K., & Moore, D. J. (2019, February). *Perceived cognitive difficulties among middle-aged to older adults living with HIV: Longitudinal associations with global cognitive functioning and depressive symptoms*. Poster session presented at the 47th annual meeting of the International Neuropsychological Society, New York, NY.

19. **Paolillo, E. W.**, Mercier, P., Godino, J., & Moore, D. J., (2018, October). *Heavy drinking and antiretroviral adherence don't mix: Assessing real-time relationships using ecological momentary assessment and wearable alcohol biosensors*. Poster session presented at the 2018 annual UC San Diego Chancellor's Research Excellence Scholarships Symposium, San Diego, CA.

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

21. Sundermann, E.E., Levine, A. J., **Paolillo, E. W.**, Masliah, E., Adame, A., Gouaux, B., Soontornniyomkij, V., Letendre, S., & Moore, D. J. (2018, September). *The relationship between synaptodendritic neuropathology and HIV-associated neurocognitive disorders is moderated by age*. Paper session presented at the 9th International Workshop on HIV & Aging, New York, NY.

22. Saloner, R., **Paolillo, E. W.**, Umlauf, A., Moore, D. J., Heaton, R. K., Grant, I., & Cherner, M. (2018, August). *Is alcohol neuroprotective in methamphetamine-associated neuropsychological impairment?* Poster session presented at the 126th annual APA Convention, San Francisco, CA.

23. **Paolillo, E. W.**, Inkelis, S. M., Heaton, A., Saloner, R. Moore, R. C., & Moore, D. J. (2018, June). *Age of remote alcohol use disorder diagnosis relates to processing speed in older adults living with HIV*. Poster session presented at the 41st annual meeting of the Research Society on Alcoholism, San Diego, CA.

24. Saloner, R., **Paolillo, E. W.**, Moore, D. J., Heaton, R. K., Grant, I., Cherner, M. & the TMARC Group (2018, June). *Neurocognitive performance among methamphetamine users depends on history of at-risk alcohol consumption*. Poster session presented at the 41st annual meeting of the Research Society on Alcoholism, San Diego, CA.

25. Saloner, R., **Paolillo, E. W.**, Moore, D. J., Heaton, R. K., Grant, I., & Cherner, M. (2018, June). *Life-time alcohol consumption conditionally relates to neurocognitive performance based on methamphetamine dependence*. Poster session presented at the 80th annual meeting of the College on Problems of Drug Dependence, San Diego, CA.

26. Saloner, R., Campbell L., Serrano, V., Montoya, J. L., Pasipanodya, E., **Paolillo, E. W.**, Franklin, D., Heaton, R. K., Moore, D. J., & the HNRP Group (2018, April). *Cognitive SuperAging in persons living with HIV: Demographic, neuromedical, and everyday functioning correlates*. Poster session presented at the UC San Diego 13th Annual Judd Young Investigators Research Symposium, San Diego, CA.

27. Rooney, A. S., Moore, R. C., **Paolillo, E. W.**, Gouaux, B., Umlauf, A., Letendre, S. L., Jeste, D. V., Moore, D. J., and the HIV Neurobehavioral Research Program (April, 2018). *Depression and aging with HIV: Associations with health-related quality of life and positive psychological factors*. Poster presented at the UC San Diego 13th Annual Judd Young Investigators Research Symposium, San Diego, CA.

28. Montoya, J. L., Pasipanodya, E. C., **Paolillo, E. W.**, Rooney, A. S., Gouaux, B., & Moore, D. J. (2018, April). Superior dose timing is related to HIV undetectability among PLWHA who use methamphetamine. In Jennifer B. Levin (chair), "*Customized Adherence Interventions for Complex and Challenging Clinical Populations.*" Symposium conducted at the 39th Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine, New Orleans, LA.

29. **Paolillo, E. W.,** Pasipanodya, E. C., Heaton, R. K., & Moore, D. J. (2018, February). *Depressive symptoms are associated with cognitive decline in HIV/AIDS*. Poster session presented at the 46th annual meeting of the International Neuropsychological Society, Washington, DC.

30. Oppenheim, H., **Paolillo, E. W.**, Moore, R. C., Ellis, R. J., Letendre, S. L., Jeste, D. V., Grant, I., & Moore, D. J. (2017, October). *HIV and aging: Can we use a frailty index as a predictor of worse neurocognitive functioning?* Poster session presented at the NeuroHIV in the ART Era Meeting, Washington, DC.

31. **Paolillo, E. W.**, Pasipanodya, E. C., Heaton, R. K., & Moore, D. J. (2017, June). *Depressive symptoms account for relationship between complex motor performance and problematic alcohol use among people living with HIV/AIDS.* Poster session presented at the 40th annual meeting of the Research Society on Alcoholism, Denver, CO.

32. Rabin, L., Bergdoll, R., Hadjisolomou, S., Ghahramani, Z., Drake, J., **Paolillo, E.**, & Walder, D. (2017, June). *Pairing mentored research with statistics and journal club didactics to maximize learning outcomes for undergraduates*. Poster session presented at the annual Council on Undergraduate Research's Undergraduate Research Collaborations Conference, Flagstaff, AZ.

33. Heaton, A., Moore, R. C., **Paolillo, E.,** Rooney, A., Jeste, D. J., & Moore, D. J. (2017, March). *Patient report vs "objective measures" in predicting everyday functioning outcomes in HIV+ adults*. Poster session presented at the 38th annual meeting of the Society of Behavioral Medicine, San Diego, CA.

34. **Paolillo, E. W.**, Gongvatana, A., Heaton, R. K., Letendre, S. L., & Moore, D. J. (2016, June). *High-level alcohol use relates to antiretroviral therapy non-adherence in adults living*

with HIV/AIDS. Poster session presented at the 39th annual meeting of the Research Society on Alcoholism, New Orleans, LA.

35. **Paolillo, E. W.**, Elbulok-Charcape, M. M., Barr, W. B., & Rabin, L. A. (2016, February). *Utilization of instruments with alternate/parallel test forms among clinical neuropsychologists in the U.S. and Canada.* Poster session presented at the 44th annual meeting of the International Neuropsychological Society, Boston, MA.
36. Blackmore, M. A., Van Ameringen, M., & **Paolillo, E. W.** (2015, April). *Mobile mental health apps: What clinicians need to know.* Workshop presented at the 35th annual conference of the Anxiety and Depression Association of America, Miami, FL.
37. Blackmore, M. A., Rego, S. A., Baker, J., Berry, S., & **Paolillo, E. W.** (2015, April). *Navigating the internship match process.* Workshop presented at the 35th annual conference of the Anxiety and Depression Association of America, Miami, FL.
38. Blackmore, M. A. & **Paolillo, E. W.** (2014, September). *Digital health technology in action: Front-line perspectives.* Webinar presented for the Center for Health Care Strategies, Inc., Hamilton, NJ.
39. **Paolillo, E. W.** (2014, July). *Cognitive Behavioral Therapy (CBT) for older adults.* Presented at Montefiore Medical Center Department of Psychiatry Education Symposium, Bronx, NY.
40. **Paolillo, E. W.** & Crump, M. J. C. (2014, April). *Skill acquisition in typing: Roles of implicit and explicit memory.* Oral presentation at the National Conference for Undergraduate Research, Lexington, KY.
41. **Paolillo, E. W.** & Crump, M. J. C. (2013, October). *10,000 hours in 10 minutes: Memory for sequence learning.* Poster presented at the 2013 National Research Experience for Undergraduates Symposium, Arlington, VA.

ABSTRACT OF THE DISSERTATION

Using Ecological Momentary Assessment to Improve Assessment of Self-Reported Cognitive Difficulties among Adults with Comorbid HIV and Heavy Alcohol Use

by

Emily Waller Paolillo

Doctoral of Philosophy in Clinical Psychology

University of California, San Diego, 2021
San Diego State University, 2021

Professor David J. Moore, Chair

Rationale: Heavy alcohol use is prevalent among people with HIV (PWH) and increases risk for neurocognitive and everyday functioning impairments. Although self-reports of cognitive difficulties are often used clinically to screen for neurocognitive impairment, such retrospective measures are subject to recall error and response bias. Thus, in a sample of PWH who were heavy alcohol drinkers, this study aimed to: 1) evaluate psychometric properties of real-time self-reported cognitive difficulties assessed via smartphone-based ecological

momentary assessment (EMA), and 2) examine temporal relationships among EMA self-reported cognitive difficulties, alcohol use, mood, and daily activities.

Design: Participants were 23 PWH recruited from existing studies at the HIV Neurobehavioral Research Program who reported current heavy alcohol use. Participants completed two in-person visits separated by a 14-day EMA monitoring period with up to four surveys per day. Objective neurocognition was measured in person by the NIH Toolbox Cognition Battery. Multiple regressions examined whether the proportion of surveys on which participants reported cognitive difficulties related to objective neurocognitive functioning. Mixed effects logistic regressions examined whether EMA-reported alcohol use, depressive symptoms, and cognitively demanding activities related to concurrent EMA-reported cognitive difficulties.

Results: Participants were 83% adherent to the EMA surveys on average. Higher proportions of surveys reporting cognitive difficulties were significantly associated with worse objective neurocognitive functioning ($p = 0.040$); however, EMA-reported real-time cognitive difficulties were not significantly more sensitive or specific in identifying objective neurocognitive impairment compared to an in-person retrospective measure (ps > 0.05). Greater EMA-reported alcohol use (OR = 1.37; $p < 0.001$) and depressive symptoms (OR = 1.80; $p = 0.016$) were significantly related to higher likelihood of concurrent cognitive difficulties within persons. EMA-reported engagement in cognitively demanding activities was related to a lower concurrent likelihood of attention difficulties within persons (OR = 0.54; $p = 0.032$).

Conclusions: EMA-reported cognitive difficulties were strongly related to real-time psychological/behavioral factors within persons. Additionally, the association between EMA-reported cognitive difficulties and objective neurocognition suggests that assessing cognitive

difficulties in real time via EMA may have some clinical utility to identify individuals from this population who need early intervention and potentially a higher level of care.

1. INTRODUCTION

Heavy alcohol use is a major risk factor for acquiring and transmitting HIV (Shuper, Joharchi, Irving, & Rehm, 2009) and the two commonly co-occur (Byrd et al., 2011; Cook & Clark, 2005; Galvan et al., 2002; Petry, 1999). Alcohol is the most frequently used and abused substance among people with HIV (PWH), with almost half of PWH having a lifetime history of alcohol dependence (Byrd et al., 2011). While the rate of any alcohol use among PWH (i.e., about 54%) is comparable to that of the general U.S. population (Substance Abuse and Mental Health Services Administration (SAMHSA), 2015), heavy drinking is substantially more prevalent among PWH with estimated rates ranging from 8% to 37% (Galvan et al., 2002). Heavy alcohol use and HIV disease are each associated with deficits in neurocognitive functioning (Antinori et al., 2007; M. E. Bates, Bowden, & Barry, 2002; Heaton et al., 2004), and when comorbid, the combination of heavy alcohol use and HIV disease puts individuals at a much higher risk for neurocognitive impairment (Gongvatana et al., 2014; Green, Saveanu, & Bornstein, 2004; Rothlind et al., 2005; Woods et al., 2016). Thus, comprehensive clinical care for persons with co-occurring HIV disease and heavy alcohol use should include strategies for early detection and monitoring of neurocognitive impairments.

1.1 Neurocognitive and Everyday Functioning among People with HIV

Although overall severity of neurocognitive impairment among PWH has significantly decreased since the advent of combination antiretroviral therapy (CART) (Heaton et al., 2011), HIV-associated neurocognitive disorders (HAND) still affect between 30-50% of PWH (Heaton et al., 2010). The neurobiological mechanisms by which HIV is likely to cause neurocognitive deficits are important to consider in the context of the relatively high prevalence of HAND. Even

in the early stages of infection, HIV is known to enter the central nervous system (CNS) via infected monocytes and macrophages. Once infected, these peripheral immune cells release neurotoxic viral proteins that weaken the integrity of the blood brain barrier (Resnick, Berger, Shapshak, & Tourtellotte, 1988; Toborek et al., 2005) and cause a cascade of neuroinflammatory events that can lead to synaptodendritic injury and neuronal apoptosis (Cody & Vance, 2016; Ellis, Langford, & Masliah, 2007). Despite CART's impressive ability to suppress viral replication in the periphery, many antiretrovirals are unable to effectively penetrate the CNS (Letendre et al., 2008), leaving reservoirs of HIV in the brain that can lead to chronic inflammation and subsequent adverse neurologic and neurocognitive consequences (Carvalhal et al., 2016).

Frontostriatal networks and the hippocampus seem to be particularly affected in HIV disease (D. J. Moore et al., 2006), which correlate with certain neurocognitive deficits most commonly seen among PWH. Specifically, in the CART era, PWH often demonstrate neurocognitive domain-specific deficits in executive functioning, learning, and memory (Heaton et al., 2011). However, because HIV is a complex illness that often presents comorbidly with a myriad of other conditions that affect neurocognitive functioning (e.g., substance use, vascular, metabolic, co-infection, cancer, psychiatric) (R. D. Moore, Gebo, Lucas, & Keruly, 2008), the profile of neurocognitive deficits is often not very consistent across individuals with HIV. Thus, deficits across a range of neurocognitive domains may be seen, depending on host and viral factors, as well as type and severity of medical and psychiatric comorbidities.

Furthermore, although these HIV-associated neurocognitive impairments are typically mild, impairments in everyday functioning are prevalent (Heaton et al., 2004). Deficits in everyday functioning may be due to a number of factors beyond neurocognitive impairment

(e.g., mood, apathy, substance use, physical ailments; (Christensen et al., 2017; Kamat et al., 2012; Kordovski, Tierney, & Woods, 2019; Sadek, Vigil, Grant, Heaton, & Group, 2007)); however, it is important to distinguish those everyday functioning deficits related to neurocognitive impairment (e.g., difficulty with grocery shopping due to memory problems) for accurate diagnosis of neurocognitive disorders (Antinori et al., 2007; Kordovski et al., 2019). Additionally, neurocognitively impaired PWH often perform worse on objective, lab-assessed measures of everyday functioning compared to neurocognitively intact PWH (Cattie et al., 2012; Doyle et al., 2013; Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Heaton et al., 2004). Impairment in the neurocognitive domains of learning, executive function, working memory, and verbal abilities are most strongly associated with deficits in everyday functioning (Heaton et al., 2004). Importantly, challenges in everyday functioning typically reflect high-stakes outcomes such as unemployment, dependence in instrumental activities of daily living (IADLs), and poor antiretroviral therapy (ART) adherence (Thames, Kim, et al., 2011), which pose risks for both declining individual health and transmission of HIV (Bangsberg, Kroetz, & Deeks, 2007).

1.2 Neurocognitive and Everyday Functioning among Heavy Drinkers

The long-term neurocognitive effects of alcohol use vary as a function of pattern and quantity consumed. The commonly referenced "j-curve" depicts the mildly beneficial effects of light to moderate alcohol use on cognitive and physical health in comparison to alcohol abstainers, and the increasing detrimental effects of heavy alcohol use with increasing quantity consumed (Eckardt et al., 1998; Lang, Wallace, Huppert, & Melzer, 2007; Neafsey & Collins, 2011; Plunk, Syed-Mohammed, Cavazos-Rehg, Bierut, & Grucza, 2014). Research estimates that about half of heavy drinkers have at least mild neurocognitive deficits (Oscar-Berman &

Marinkovic, 2007), and that alcohol-related neural injury seems to be best predicted by recency and frequency of heavy drinking (Sullivan & Pfefferbaum, 2005). Current evidence supports the theory that heavy alcohol use causes neural and glial degeneration and atrophy by increasing oxidative stress, inducing a proinflammatory cascade, and potentially inhibiting neural and glial generation (Crews & Nixon, 2009; Nixon, 2006). Among chronic heavy drinkers, reduced white and gray matter volumes are often seen in the frontal lobes, with associated damage to important frontal circuitry including frontocerebellar, frontostriatal, and corticolimbic pathways (Sullivan et al., 2003; Sullivan & Pfefferbaum, 2005). This results in a pattern of neurocognitive impairment characterized by deficits in executive functioning, processing speed, visuospatial abilities, gait, and balance (Oscar-Berman & Marinkovic, 2007; Sullivan & Pfefferbaum, 2013).

Notably, both the acute (i.e., during alcohol intoxication and withdrawal/hangover) and chronic (i.e., long-term damage from chronic alcohol use) neurocognitive impairments among heavy alcohol users contribute to impairments in everyday functioning with significant disruptions in psychosocial functioning. First, as in many addictive disorders, alcohol-related executive dysfunction (e.g., poor planning, inhibition, lack of future-oriented behavior) promotes continued heavy alcohol use despite awareness of associated problems, and can interfere with success of treatment for alcohol use disorders (Houston et al., 2014; van Deursen et al., 2015). Furthermore, heavy alcohol use is often associated with increased rates of disability, unemployment, financial and housing instability, and social distress (M. E. Bates et al., 2002; Compton, Gfroerer, Conway, & Finger, 2014; Peirce, Frone, Russell, Cooper, & Mudar, 2000).

1.3 Comorbid HIV and Heavy Alcohol Use

Dual presentation of HIV and heavy alcohol use is associated with increased likelihood of poor HIV disease outcomes (Azar, Springer, Meyer, & Altice, 2010). The combined neurotoxic effects of HIV disease and heavy alcohol use can lead to increased neuronal injury that preferentially targets the corpus callosum and frontal white matter (Pfefferbaum, Rosenbloom, & Sullivan, 2002; Pfefferbaum, Rosenbloom, Adalsteinsson, & Sullivan, 2007; Pfefferbaum et al., 2006), resulting in an increased prevalence of neurocognitive impairment compared to those with either condition alone (Gongvatana et al., 2014; Green et al., 2004; Rothlind et al., 2005; Woods et al., 2016). Exact neurobiological mechanisms underlying the additive or synergistic detrimental effects of HIV and heavy alcohol use on neurocognitive functioning are not well understood. Ways in which heavy alcohol use may exacerbate HIV-associated neurocognitive dysfunction include decreased adherence to CART (Hendershot et al., 2009, Paolillo et al., 2017) and greater alcohol-induced immunosuppression, which can lead to higher HIV viral load and increased risk for HIV-associated neuronal damage in selectively vulnerable areas (Woods et al., 2009, Rosenbloom et al., 2010). Conversely, HIV may also exacerbate alcohol-related neurocognitive dysfunction via a wide range of partially overlapping mechanisms. Heavy alcohol use may reduce brain reserve, further increasing the vulnerability of individuals to HIV-related neurocognitive impairment once infected (Gongvatana et al., 2014). Additionally, liver damage acquired from heavy alcohol use may increase the risk of neuronal damage via minimal hepatic encephalopathy (Schiff et al., 2014), hyperammonemia, increased inflammation (Felipo et al., 2012), and reduced ability to metabolize CART, thus increasing neurotoxicity (Moore et al., 2007). These alcohol-induced changes are likely to make individuals more vulnerable to neurocognitive impairment in the context of HIV.

The profile of neurocognitive impairment among PWH who drink heavily represents a combination of neurocognitive domains affected in each condition alone, and is characterized by deficits in executive functioning, working memory, visuospatial skills, processing speed, and motor skills (Farinpour et al., 2000; Persidsky et al., 2011; Pfefferbaum et al., 2007; Rothlind et al., 2005). This pattern of neurocognitive impairments puts PWH who drink heavily at greater risk for impairments in everyday functioning, including worse HIV medication management, and unemployment (Rothlind et al., 2005). Despite the significant public health concerns (e.g., HIV transmission risk) and economic burden (e.g., unemployment, marginal housing) following neurocognitive and everyday functioning impairments among persons with HIV who drink heavily (United Nations, 2004), no reliable and valid method exists to identify those at risk for neurocognitive impairment and associated "real-world" functional difficulties without a full neuropsychological evaluation.

1.4 Evaluation of Cognitive Difficulties

Brief, reliable, and valid measures of neurocognitive and everyday functioning are growing in demand among both research and clinical settings (Finkel, 2003). Although neuropsychological evaluations are necessary for diagnosis of HIV-associated neurocognitive disorders (Antinori et al., 2007), the time and expense associated with administration of a full neuropsychological battery prevent their use in many settings (Carey, Woods, Rippeth, et al., 2004). Clinically, health care providers would substantially benefit from being able to identify patients in greatest need of full neuropsychological evaluation by accurately assessing functional cognitive difficulties experienced in real time during a person's regular daily activities. Such assessments would additionally allow researchers and clinicians to be able to monitor individuals

in-between full evaluative visits. The ability to accurately and cost-effectively screen for early changes in neurocognitive and functional status is a critical step towards being able to provide optimal care and treatment for individuals in this population.

Self-report measures hold promise in briefly assessing for neurocognitive impairment-related difficulties with everyday functioning (i.e., cognitive difficulties) among people with HIV who drink heavily; however, common and well-documented response biases in retrospective self-report measures (e.g., recall errors, social desirability effects, cognitive deficits, lack of insight, or state dependent bias) limit their use (Roberts, Clare, & Woods, 2009). For example, depression has been shown to be strongly associated with greater endorsement of cognitive difficulties because of the tendency for individuals with depression to have inaccurately low self-appraisals of past performance (Thames, Becker, et al., 2011). Furthermore, previous research estimates that up to 50% of PWH show poor insight into their neurocognitive and functional abilities when using traditional retrospective self-report assessments (e.g., the Patient Assessment of Own Functioning Inventory) (Hinkin et al., 1996), and this may be worsened in those PWH who have co-occurring alcohol or other substance use disorders (Casaletto et al., 2015; Walvoort, van der Heijden, Wester, Kessels, & Egger, 2016).

Despite known response biases, several studies have revealed independent associations between slef-reported cognitive difficulties and neuropsychological performance, even in the context of depression and medical symptoms (Amariglio, Townsend, Grodstein, Sperling, & Rentz, 2011; Carter, Rourke, Murji, Shore, & Rourke, 2003; Hulur, Hertzog, Pearman, Ram, & Gerstorf, 2014). This suggests that reducing bias by diminishing retrospective recall error and improving ecological validity has the potential to improve the utility of such self-report measures. Therefore, modifying and improving the timeframe and method by which we assess

for these risks may have a wide range of positive implications for early detection, and subsequent treatment and rehabilitation of neurocognitive and everyday functioning impairments.

1.5 Ecological Momentary Assessment

Ecological momentary assessment (EMA) is an assessment methodology that can enhance reliability and validity when measuring subjective symptoms and experiences (Shiffman, Stone, & Hufford, 2008). By collecting data in real time, EMA has been shown to increase ecological validity and reduce bias and retrospective recall errors (Shiffman et al., 2008; van den Brink, Bandell-Hoekstra, & Abu-Saad, 2001). EMA's ability to improve sensitivity to change was shown in one study by Raeanne Moore, Ph.D., and colleagues that used daily EMA surveys to assess changes in mood before and after participation in one of two interventions (i.e., Mindfulness-Based Stress Reduction or health education) among emotionally distressed older adults (R. C. Moore, Depp, Wetherell, & Lenze, 2016). Results demonstrated not only that participants were highly responsive to and accepting of these daily assessments, but also that EMA was more likely to detect to changes in mood compared to standard administration of the same items at pre- and post-intervention study visits. Furthermore, results from EMA studies also suggest that the aggregate mean EMA score of reported symptoms is likely to be more accurate than the single reporting at one time point, which is often influenced by factors noted above (e.g., retrospective recall error, state-dependent bias) (R. C. Moore, Depp, et al., 2016) (**Figure 1**).

Another beneficial aspect of EMA is the ability to capture daily, or moment-to-moment variability in an individual's self-reported functioning, providing additional information that may be more useful in identifying risks for functional difficulties compared to relying on aggregate

data or retrospective information gathered at one time-point. This was clearly demonstrated in a previous study that used EMA to assess subjective impulsivity and risk for mania in patients with bipolar disorder (Depp et al., 2016). Time-lagged model analysis of data collected via twice-daily EMA surveys over 11 weeks revealed that within-person increases in negative affect (but not positive affect) predicted within-person increases in subjective impulsivity. This was in contrast to the examination of an aggregate mean rating of subjective impulsivity, which showed that average manic (but not depressive) symptoms predicted subjective impulsivity between persons. These results highlight the importance of real-time information collected via EMA in the examination of real-world associations and functioning.

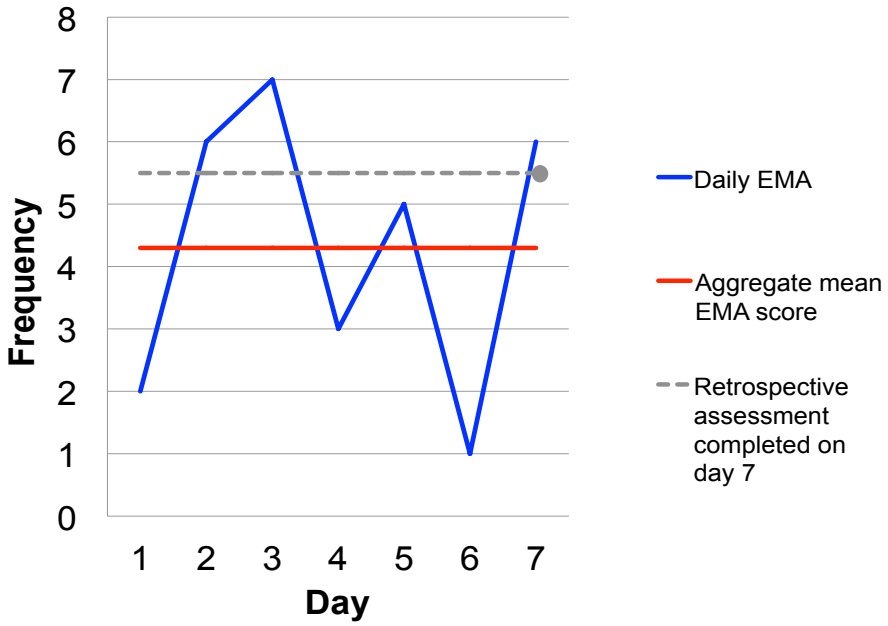

Figure 1. Example of aggregate mean EMA score compared to score from a retrospective assessment.

1.6 Feasibility of EMA among PWH who Drink Heavily

In particular, *smartphone*-based EMA is likely to be an easily implemented and feasible method for use among PWH, even those who drink heavily. Smartphone use is near ubiquitous in present day, with results from a 2021 national survey estimating that about 85% of U.S. adults aged 18 years and over own smartphones (Pew Research Center, 2021), and that smartphone ownership continues to increase. While adherence to EMA surveys is one potential concern when utilizing this repeated assessment method among heavy alcohol and substance users, previous research has shown excellent EMA adherence among alcohol and substance using populations, even when individuals are homeless (Shiffman, 2009). Several recent studies have also estimated high rates of EMA adherence among PWH, even among older PWH who may be relatively more smartphone-naïve than younger counterparts (R. C. Moore, Kaufmann, et al., 2016; Paolillo et al., 2017).

One recent pilot study specifically assessed the feasibility and acceptability of daily EMA among older PWH recruited from the HIV Neurobehavioral Research Program (HNRP) (R. C. Moore et al., 2017). Specifically, this pilot study examined the use of EMA to assess everyday functioning in a sample of 20 older PWH. Over the course of one week, participants received five EMA surveys per day assessing current activity, productivity, mood, medication adherence, and substance use. Results indicated high rates of EMA survey completion, with participants completing an average of 30 out of the 35 total surveys (86% compliance). Participants also reported high satisfaction with the EMA experience in response to the post-study feedback item (i.e., "I enjoyed the experience"), with a mean rating of 3 on a scale of 0 ("Not at all") to 4 ("Very much"). Additionally, results of the pilot study showed a significant negative relationship ($r = -0.57$, $p < 0.01$) between EMA-measured time spent in passive leisure activities (i.e.,

watching TV) and lab-based neurocognitive functioning as measured by the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS), supporting the hypothesis that EMA-administered self-report surveys are capable of detecting differences in objectively measured neurocognitive functioning among PWH (**Figure 2**). Additional studies since then have repeated these feasibility findings in other samples (e.g., (L. M. Campbell et al., 2020).

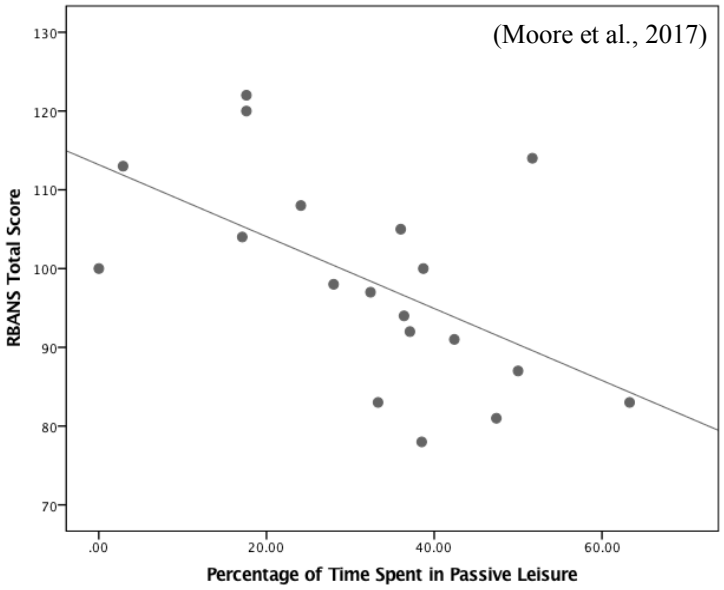

Figure 2. Greater EMA-measured time spent in passive leisure activities relates to worse cognitive functioning (Moore et al., 2017).

Furthermore, another recent EMA study of PWH found that alcohol and substance use demonstrated convergent validity with alcohol and substance use assessed via a timeline follow-back interview among older adults (Paolillo et al., 2017). Results also indicated temporal relationships among alcohol and substance use, mood, and pain, demonstrating ability to detect time-varying changes in subjective experiences based on alcohol use and mood via EMA data. Consistent with Dr. RC Moore's previous EMA study, participants had high rates of survey

completion (89.5%). Importantly, EMA adherence was not related to either alcohol/substance use or demographics, suggesting lack of selection bias. While this supports the validity of self-reported alcohol and substance use via EMA, future studies may still benefit from an exploration of methods to measure alcohol use more objectively (e.g., via a wearable or personal portable breathalyzer). Still, these results demonstrate the high feasibility and acceptability of daily EMA among PWH, further supporting use of EMA in this population.

Despite many documented strengths of symptom monitoring via EMA, there is currently no research examining the use of daily EMA surveys assessing cognitive difficulties to identify risk for neurocognitive impairment, even in such high-risk populations as individuals with HIV and heavy alcohol use. The current international recommendation to briefly assess risk for HIV-associated neurocognitive impairment in clinical settings includes the administration of three self-report questions developed by the European AIDS Clinical Society (EACS) that assess for problems with memory, processing speed, and attention (European AIDS Clinical Society, 2015). Although these questions have been shown to adequately identify symptomatic neurocognitive impairment, the retrospective self-report nature of these questions can lead to inaccurate identification of PWH with neurocognitive impairment who may have biased responses and do not report cognitive difficulties in daily life (Metral et al., 2020). Thus, repeated assessment of the EACS questions via EMA may reduce bias and improve ability to identify risk of milder cognitive impairments by allowing individuals to report cognitive difficulties in real time.

1.7 Understanding Other Factors Affecting Cognitive Difficulties

Importantly, EMA can also allow us to gain a deeper understanding of various time-varying factors that may influence the experience of cognitive difficulties in real-time (e.g., alcohol use, mood, engagement in cognitively demanding activities) so that we may be able to control for them and make better predictions when using self-reported cognitive difficulties to screen for neurocognitive impairment. This is especially important in the context of alcohol use, as it is unknown how the acute neurocognitive effects of heavy alcohol use (Oscar-Berman & Marinkovic, 2007) relate to an individual's appraisal of their overall cognitive functioning. In addition, engagement in cognitively demanding activities is important to consider when examining subjective cognition, as it is possible that individuals with objective neurocognitive impairment may not encounter cognitive difficulties in their daily lives if they never participate in activities that challenge them cognitively; however, this has not been specifically examined in previous studies. To aid our understanding of these within person relationships, it may also be important to explore the feasibility and validity of using an *objective* measure of alcohol use in a person's real-world setting.

Thus, this study aimed to both examine the psychometric properties of the EACS neurocognitive screening questions administered via smartphone-based EMA and explore temporal relationships among alcohol use, mood, cognitively demanding activities, and cognitive difficulties among PWH who drink heavily. Information gathered from this study may have implications for improving early detection of neurocognitive and everyday functioning impairments, an essential component of providing optimal treatment and care in HIV and heavily-drinking populations. Furthermore, the EMA method under investigation in this study has considerable potential to be implemented in a variety of clinical settings and contexts (e.g.,

an app to track cognitive difficulties and/or alcohol use before/between clinical appointments). Therefore, the study proposes an innovative contribution to alcohol use, neuroAIDS, and assessment literatures that can inform future development of mobile assessments for detection of neurocognitive and everyday functioning impairments in other populations.

1.8 Purpose and Specific Aims

Several studies have found independent associations between self-reported cognitive difficulties and neuropsychological performance; however, weaknesses in previous methodologies (e.g., known self-report response biases, small effect sizes characterizing the relationship between retrospective self-reported cognitive difficulties and objective neurocognition) support attempts to improve the method by which we assess cognitive difficulties. Specifically, self-reported cognitive difficulties may be more accurately evaluated using real-time, real-world assessment methods such as EMA. By asking individuals to report their current functioning several times per day, we may be able to substantially reduce response biases. Additionally, using this methodology, we can examine real-time predictors of self-reported cognitive difficulties (e.g., alcohol use, mood, engagement in cognitively demanding activities), allowing us to further understand and control for factors that may lead to discrepant subjective and objective cognitive functioning. Thus, this dissertation study aimed to: 1) evaluate self-reported cognitive difficulties (reported via EMA) as a predictor of neurocognitive functioning among PWH who drink heavily, and 2) examine real-time temporal relationships between level of alcohol use, mood, engagement in cognitively demanding activities, and reports of cognitive difficulties. We also uniquely explore the acceptability, feasibility, and validity of a portable alcohol breathalyzer for a more objective measure of alcohol use. Ultimately, the

knowledge gained from this study will help clarify whether monitoring cognitive symptoms via EMA may improve identification of neurocognitive and everyday functioning impairments. If successful, this method could be used in a wide variety of settings (e.g., clinical, research) and contexts (e.g., urban, rural) and potentially improve the treatment services that patients in this vulnerable population receive.

Aim 1. Evaluate psychometric properties of the EMA-administered EACS screening questions. Over a period of 14 days, participants completed four EMA surveys per day (i.e., up to 56 surveys total) that included the EACS screening questions asking them to report their experience of cognitive difficulties since the last survey. Participants also completed standard paper-and-pencil administration of EACS questions at the in-person baseline visit. ***Hypothesis 1a:*** Responses to EMA-administered EACS items will show convergent validity with performance on neurocognitive tests. ***Hypothesis 1b:*** Responses to EMA-administered EACS items will be more sensitive and specific in identifying those with and without neurocognitive impairment compared to that of EACS standard administration.

Aim 2. Examine alcohol use, mood, engagement in cognitively demanding activities as real-time predictors of cognitive difficulties. EMA surveys also included items asking participants to report the number of alcoholic beverages consumed since the last survey, level of current depressed mood, and whether they engaged in any cognitively demanding activities since the last survey. ***Hypothesis 2a:*** Greater alcohol use will be associated with a higher likelihood of concurrent (i.e., same survey) and future (i.e., subsequent surveys) cognitive difficulties. ***Hypothesis 2b:*** Greater depressed mood will be related to higher likelihood of concurrent cognitive difficulties. ***Hypothesis 2c:*** Engagement in cognitively demanding activities will be

related to higher likelihood of concurrent cognitive difficulties only in the context of objective neurocognitive impairment.

Exploratory Aim. Examine acceptability, feasibility, and validity of an objective measure of alcohol use during the EMA monitoring period (i.e., a portable alcohol breathalyzer).

2. METHODS

2.1 Participants

The final sample of participants in this study were 23 PWH who reported current heavy alcohol use in the last 30 days per National Institute on Alcohol Abuse and Alcoholism (NIAAA) guidelines (i.e., >3 drinks per day or >7 drinks per week for women; >4 drinks per day or >14 drinks per week for men). Participants were primarily recruited from the larger NIH-funded grants and centers within the UC San Diego HIV Neurobehavioral Research Program (HNRP; e.g., HIV Neurobehavioral Research Center [HNRC; NIMH P30MH062512]; Translational Methamphetamine AIDS Research Center [TMARC; NIDA P50DA026306]), as well as from one previous alcohol-related study conducted at the HNRP (NIAAA K99/R00 AA020235). See section 2.3 ("Recruitment Procedures") for a full description of the recruitment and enrollment process. We chose to examine our paradigm in the context of HIV and heavy alcohol use because of the high prevalence of comorbidity, the considerably increased risk for neurocognitive and everyday functioning impairments, and the subsequent public health significance in this high-risk group (e.g., high HIV transmission risk).

2.2 Participant Characterization and Inclusion/Exclusion Criteria

Inclusion criteria for this study were: 1) HIV seropositive status; 2) self-reported current heavy alcohol use (per NIAAA guidelines) within the 30 days prior to the baseline visit; 3) fluency in English; and 4) capacity to provide written informed consent to participate. HIV serostatus was determined by data from parent-study visits which used either rapid testing or enzyme-linked immunosorbent assay (ELISA) and a confirmatory Western Blot. Current heavy alcohol use was defined according to NIAAA guidelines for high-risk drinking (i.e., >3 drinks

per day or >7 drinks per week for women; >4 drinks per day or >14 drinks per week for men) and was determined by a brief timeline follow-back interview assessing alcohol use within the 30 days prior to the baseline visit. Potential participants were excluded from this study if they met Diagnostic and Statistical Manual (4th ed.; DSM-IV) (American Psychiatric Association, 1994) criteria for current dependence on any non-alcohol substance (e.g., cocaine) within the last year. Other exclusion criteria included history of severe learning disability (i.e., history of diagnosis or current standard score <70 on the Wide Range Achievement Test–4) (Wilkinson & G.J., 2006), history of a psychotic disorder unrelated to substance use (e.g., schizophrenia), and major neurological conditions known to affect cognitive functioning (e.g., stroke). Participants who tested positive for alcohol on a Breathalyzer test or who screened positive for illicit drugs (excluding marijuana) on a urine toxicology screen at the baseline visit were rescheduled for another day. In an effort to minimize selection bias, smartphone ownership was not criteria for inclusion. In the event that a participant did not have their own smartphone, one was provided to the participant free of charge along with a data plan that allowed them to complete the EMA surveys. UC San Diego IRB approval was obtained for the current study, and all participants provide written informed consent.

2.3 Recruitment Procedures

Potential study participants (i.e., participants who were likely to meet inclusion and exclusion criteria) were identified based on data collected as part of their parent study visit. These potential participants were either approached on the day of their parent HNRP study visit or were contacted via phone to evaluate their interest in participating in the current study for compensation. All potential participants had already signed IRB-approved HNRP study consents,

which include language confirming their willingness to be approached and/or contacted for participation in additional studies. We identified and attempted to contact 174 potential participants. Of these 174 attempted contacts, we enrolled a total of 26 participants (15%). These recruitment efforts were completed from January 2019 to February 2020, which was before the start of the COVID-19 pandemic. This low enrollment rate reflects a number of recruitment difficulties, including 80 (46%) individuals who we were unable to reach (e.g., phones not in service, screened and scheduled with subsequent no-show, many voicemail messages left with no return), 30 (17%) who had reduced their alcohol intake since their last HNRP visit and no longer met alcohol use inclusion criteria, 17 (10%) who moved out of the San Diego area and could not travel, 14 (8%) who were not interested in participating, and 7 (4%) who we identified as meeting exclusion criteria (e.g., current non-alcohol substance dependence, psychotic disorder diagnosis). These recruitment difficulties likely reflect the difficult-to-engage nature of our heavy-alcohol-using study population, who often have housing and financial instability as well as comorbid psychopathology, and may thus be less willing or available to participate in research (Dee, 2001; Fazel, Khosla, Doll, & Geddes, 2008; McVicar, Moschion, & van Ours, 2015; Shiffman, 2009). Of the 26 participants who were enrolled, three did not complete the study due to barriers with psychiatric stability (i.e., severe suicidality requiring hospitalization; n=1) and engagement (i.e., non-adherence to EMA study protocol with loss of contact; n=2). This resulted in our final sample of 23 participants.

2.4 General Study Procedures

The current study involved two in-person visits at the HNRP, separated by 14 days of remote monitoring during which participants were instructed to complete four smartphone-based

EMA surveys per day accompanied by use of a portable alcohol breathalyzer at the end of each survey.

Baseline Assessments, Visit 1. All participants received the standard paper-and-pencil EACS neurocognitive screener, which included the three standard item stems: 1) *Do you experience frequent memory loss?;* 2) *Do you feel that you are slower when reasoning, planning activities, or solving problems?;* and 3) *Do you have difficulties paying attention?* Response options for each item were: a) Never; b) Hardly ever; and c) Yes, definitely. Current EACS guidelines identify individuals as at-risk of neurocognitive impairment when they respond, "Yes, definitely" to at least one item (European AIDS Clinical Society, 2015). Participants also completed additional self-report measures assessing: 1) mood via the Beck Depression Inventory-II (BDI-II; (Beck, Steer, & Brown, 1996), Beck Anxiety Inventory (BAI; (Steer & Beck, 1997), and Profile of Mood States (POMS; (McNair, Lorr, & Droppleman, 1971); 2) subjective cognitive functioning via the Patient Assessment of Own Functioning Inventory (PAOFI), which assesses frequency of experienced cognitive difficulties (Chelune, Heaton, & Lehman, 1986); 3) everyday functioning via a modified version of the Lawton and Brody Activities of Daily Living Scale (Heaton et al., 2004; Lawton & Brody, 1969), which assesses functional decline for multiple domains (e.g., household chores, finance management); 4) past year alcohol use via the Alcohol Use Disorders Identification Test (AUDIT), which is a 10-item screener to assess alcohol consumption, drinking behaviors, and alcohol-related problems. In addition, a brief timeline follow-back interview was conducted with all participants to assess alcohol use quantity and frequency of alcohol use in the last 30 days, as this is a gold-standard for retrospectively measuring alcohol use (Sobell & Sobell, 1992), (**Table 1**). To maximize accuracy of participants' estimated alcohol use quantity and frequency during our brief timeline

follow-back assessment, time was spent demonstrating measurement classifications for a "standard" drink (e.g., 12 ounces of regular beer [~5% alcohol content]; 5 ounces of wine [~12% alcohol content]; 1.5 ounces of liquor [~40% alcohol content]; (National Institute on Alcohol Abuse and Alcoholism). Similar to the training conducted during standard timeline follow-back interviews, we employed the use of pictures and props (e.g., glasses, cans) to facilitate participants' understanding of the amounts of different alcohols that equal one standard drink.

Table 1. Summary of In-Person Measures

Assessment Period	**Measures**	**Construct Assessed**	**Approximate Administration Time (min)**
Baseline	Demographic and Employment Questionnaire	Demographics	5
Baseline & Follow-Up	Beck Depression Inventory-II; Beck Anxiety Inventory; Profile of Mood States	Symptoms of depression and anxiety	15
Baseline & Follow-Up	European AIDS Clinical Society (EACS) neurocognitive screening questions; Patient Assessment of Own Functioning Inventory (PAOFI); Modified Lawton and Brody Activities of Daily Living Scale	Self-reported cognitive & everyday functioning	15
Baseline & Follow-Up	Alcohol Use Disorders Identification Test (AUDIT); Brief Timeline Follow-back Assessment of Current Alcohol Use	Alcohol Use	20
Baseline	NIH Toolbox Cognition Battery*	Objective Neurocognition	30
Follow-Up	Follow-Up Participant Satisfaction Questionnaire	EMA acceptability	5

*Only administered when a participant's last comprehensive HNRP visit was more than six months prior to the current baseline visit.

Additionally, the NIH Toolbox Cognition Battery, our primary objective measure of neurocognition, was administered to participants whose most recent NIH Toolbox assessment (i.e., during their last comprehensive HNRP visit) was more than six months prior to this baseline visit (n=15; NIH Toolbox Cognition data was linked for the remaining 8 participants). The NIH Toolbox Cognition Battery is a brief, 30-minute, computerized neurocognitive evaluation administered on an iPad (Brearly et al., 2018; Heaton et al., 2014; Weintraub et al., 2013). It consists of seven tests covering different neurocognitive domains: 1) attention and executive functioning (Flanker Inhibitory Control and Attention Test and Dimensional Change Card Sort Test); 2) episodic memory (Picture Sequence Memory Test); 3) working memory (List Sorting Working Memory Test); 4) language (Picture Vocabulary Test and Oral Reading Recognition Test); and 5) processing speed (Pattern Comparison Processing Speed Test). Test scores from all domains except language (i.e., attention and executive functioning, episodic memory, working memory, and processing speed) were used to create our primary measure of neurocognition, the composite Fluid Cognition T-score, which is fully demographically-corrected with a mean of 50 and standard deviation of 10 in the normative sample (Heaton et al., 2014). Fluid Cognition T-scores were also transformed into Fluid Global Deficit Scores (GDS) which were used to characterize severity of neurocognitive impairment (Carey, Woods, Gonzalez, et al., 2004).

Brief EMA Training, Visit 1. All participants underwent a brief training on accessing and completing EMA surveys, as well as using the portable alcohol breathalyzer. Participants were shown how to access surveys on their smartphone's web browser via web-links received through SMS text messages. Participants using study smartphones were additionally taught how to use the phone (i.e., locking and unlocking; using the text messaging and web browser apps;

turning on notifications and sound). All participants were also taught how to use the portable alcohol breathalyzer (i.e., the "BACtrack Go"; **Figure 3**) and were instructed to carry it with them for the duration of the study. Participants received additional training as needed. Participants were given an operating manual, including information on responding to EMA surveys, troubleshooting any problems with the phone, web browser, and breathalyzer, and study staff contact information. Last, participants were instructed to complete the EMA survey and use the alcohol breathalyzer four times per day for 14 days. This method was based on successfully implemented methods from previous EMA studies at the HNRP (PI: Raeanne C. Moore, Ph.D.; (Paolillo et al., 2017).

Figure 3. "BACtrack Go" portable alcohol breathalyzer used in the current study. This breathalyzer includes a keychain ring and a fold-out mouthpiece for portability.

Fourteen-day EMA Monitoring Period. EMA surveys were administered using HIPAA-compliant Qualtrics surveys for which the weblinks (accessible via smartphone web browser) were delivered via SMS text messages through the Qualtrics system. For the 14 days following their baseline visit, participants received text messages with weblinks to the online survey four times per day (**Figure 4A**), providing up to 56 timepoints per person. Participants were instructed to answer the surveys as soon as possible, as the weblinks would deactivate after

60 minutes. The EMA surveys were scheduled to be delivered at random times within four intervals (i.e., morning, midday, evening, and night). We assessed participants' sleep-wake schedules to ensure surveys were never delivered outside participants' self-identified hours awake. The EMA surveys consisted of the three EACS questions, modified slightly to fit the context of EMA-administration (**Figure 4B**)[1]. Such item alterations have been successfully utilized in Dr. RC Moore's previous research (R. C. Moore, Depp, et al., 2016).

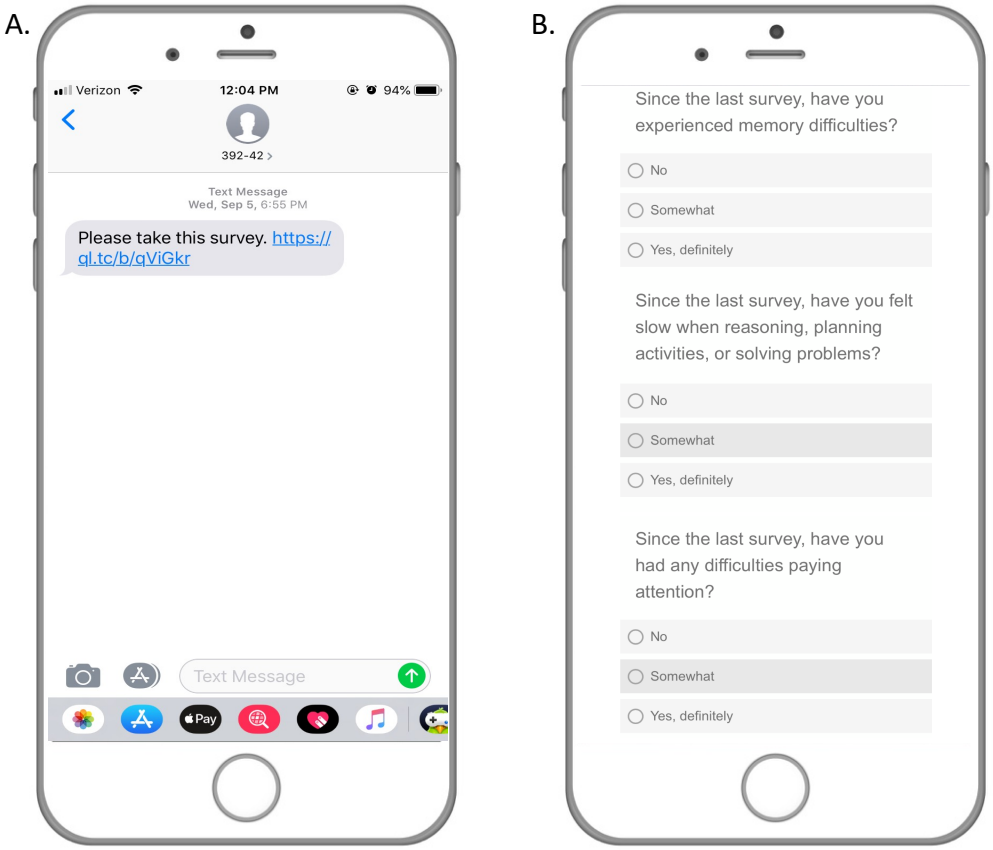

Figure 4. A) Screenshot of Qualtrics weblink delivered via text message. B) EMA survey displaying EACS neurocognitive screening questions.

[1] In order to ensure that the modified EACS response options were psychometrically equivalent to that of the standard in-person EACS questions, a modified in-person version of the EACS questions (with response options identical to that of the EMA-administered version) was also administered at baseline. Participants responded nearly identically on both versions of the EACS questions, with strong correlations between responses on the different versions of item 1 ($r = 0.87$, $p < 0.001$), item 2 ($r = 0.92$, $p < 0.001$), and item 3 ($r = 0.97$, $p < 0.001$).

The EMA survey also included brief assessments of alcohol consumption, mood, engagement in cognitively-demanding activities, pain, fatigue, and use of other non-alcohol substances (see **Appendix 1** for the full survey). The last item on each survey instructed participants to use their portable alcohol breathalyzer and record the number by choosing a numerical value from a dropdown box. Participants were also given an option to choose if they were unable to use the breathalyzer at that moment (e.g., for privacy; if they did not have the breathalyzer with them). The entire EMA survey takes about five minutes to complete. Participants were monetarily incentivized to complete surveys such that they received an extra $1 for each EMA survey completed.

Follow-Up, Visit 2. All participants returned to the HNRP for a follow-up visit after completion of the EMA monitoring period, two weeks after Visit 1. Participants completed the same self-report measures that they completed at the baseline visit (outlined in Table 1), as well as a participant satisfaction questionnaire to assess participants' experience with and acceptance of the EMA surveys and use of the breathalyzer.

2.5 Existing Neuromedical and Psychiatric Data

Embedding the current study within the HNRP enabled us to characterize the basic medical and neuropsychiatric aspects of this cohort at no cost to the current study. The standard assessments of the primary parent grants from which we recruited participants allowed us to draw upon an array of important neuromedical information, including: 1) current and nadir CD4 counts; 2) CDC HIV staging; 3) HIV RNA measured in plasma; 4) estimated number of years living with HIV; 5) current ART regimen; and 6) medical comorbidities (e.g., hepatitis C co-infection, diabetes). Additionally, all participants will have undergone a comprehensive

psychiatric evaluation during their parent study visit, which provided: 1) DSM-IV diagnoses of current and lifetime substance use and mood disorders based on the Composite International Diagnostic Interview (CIDI version 2.1) (World Health Organization, 1998); and 2) lifetime substance use quantification (onset, recency, duration, quantity, and frequency) of all substances based on a modified, semi-structured timeline follow-back interview. Of note, the DSM-IV versus the DSM 5 was utilized, as the parent grants from which subjects were drawn were funded before the DSM 5 was published. Finally, and as mentioned previously, we sourced NIH Toolbox Cognition Battery data from parent study visits when this occurred within 6 months from the current study's baseline visit. This allowed us to capture current objective neurocognitive functioning while reducing burden and minimizing practice effects for participants who had a recent HNRP visit.

2.6 Statistical Analyses

Hypothesis 1a. Responses to EMA-administered EACS items will show convergent validity with performance on neurocognitive tests. The primary neurocognitive outcome variables were derived from performance on the NIH Toolbox Cognition Battery, including: 1) continuous Fluid Cognition T scores (lower values = worse neurocognitive performance), and 2) dichotomous neurocognitive impairment status, with impairment defined by a Fluid GDS score of ≥ 0.05. The primary predictor variable was the proportion of surveys on which a participant endorsed any cognitive difficulties out of all completed surveys over the 14-day EMA monitoring period. As mentioned previously, we used a modified version of the EACS screening questions to appropriately fit the repeatedly administered EMA-context. Although cognitive difficulties on the EACS are typically identified by a response of "Yes, definitely" to any of the

three items, our modified EMA-administered EACS questions yielded a very low proportion of "Yes, definitely" responses (3%). Thus, we classified participants as endorsing cognitive difficulties on any survey in which they responded either "Somewhat" or "Yes, definitely" to any of the EACS questions. We used linear and logistic bivariate regression models to evaluate whether the proportion of surveys on which participants reported cognitive difficulties was negatively related to Fluid Cognition T-scores and neurocognitive impairment status, respectively. Given our relatively small sample size and our clear directional hypothesis, we used one-tail tests to increase power to detect an effect. Exploratory analyses were also conducted to examine the association of each individual EACS item to neurocognitive functioning (one-tailed).

Hypothesis 1b. Responses to EMA-administered EACS items will be more sensitive and specific in identifying those with and without neurocognitive impairment compared to that of EACS standard administration. We first calculated sensitivity and specificity for each administration of the EACS questions (i.e., standard and EMA), then compared these values by administration method. The primary outcome was objectively-measured neurocognitive impairment status (impaired = Fluid GDS score of ≥ 0.5). As noted previously, the standard in-person EACS questions identify risk for neurocognitive impairment when a person responds, "Yes, definitely" to any of the three items. To identify risk for neurocognitive impairment using the EMA-administered EACS questions, an ROC curve will be used to determine the optimal cut-point (i.e., proportion of surveys on which participants endorsed any cognitive difficulties) for maximizing sensitivity and specificity of detecting impairment. After calculating sensitivity and specificity for both, two McNemar's chi-squared tests for paired observations were conducted: one to compare sensitivity and one to compare specificity.

Post-hoc analyses for Hypotheses 1a and 1b. Two sets of post-hoc analyses were conducted to thoroughly examine Hypotheses 1a and 1b using different methodological approaches to scoring the NIH Toolbox Cognition and defining neurocognitive impairment. First, we repeated the primary analyses for Hypotheses 1a and 1b using demographic- and reading-corrected Fluid Cognition T scores and Fluid GDS, which adjust for NIH Toolbox Oral Reading score (Holdnack et al., 2017). The second set of analyses were conducted to address the potential problem of practice effects from repeated NIH Toolbox Cognition assessments at the HNRP, as some participants had up to five previous NIH Toolbox assessments before participating in the current study. Thus, we repeated the primary analyses for Hypotheses 1a and 1b again using participants' first-ever NIH Toolbox Cognition scores (i.e., from their first NIH Toolbox assessment at the HNRP).

Hypothesis 2a. Greater alcohol use will be associated with higher likelihood of concurrent (i.e., same survey) and future (i.e., subsequent surveys) cognitive difficulties. Mixed-effects logistic regression models were used to analyze our data structure in which four-times-daily EMA surveys were nested within participants. The primary outcome variable was a dichotomous variable representing whether the participant endorsed cognitive difficulties on each EMA survey. The primary predictor variable was the reported number of alcoholic beverages consumed since the last EMA survey (continuous). This variable was person-mean centered in order to understand how fluctuations in drinking (relative to one's average level of alcohol consumption) relate to cognitive difficulties. To model the concurrent relationship, we examined whether the number of alcoholic beverages consumed predicted cognitive difficulties as reported on the same EMA survey. To model the lagged relationship between alcohol consumption and future cognitive difficulties, we examined whether number of alcoholic

beverages consumed on one survey predicted cognitive difficulties as reported on the next survey (using a time-lagged predictor variable). For all models, time-varying (within-person) covariates included time of day (i.e., morning, midday, evening, nighttime; modeled continuously [1-4]) and study day (modeled continuously [1-14]). Time-invariant (between-person) covariates included for all models were average alcohol consumption (i.e., a participant's average number of drinks reported over the 14-day EMA monitoring period), age, and objective neurocognitive impairment. These covariates were chosen a priori due to their hypothesized relationship with the outcome (i.e., cognitive difficulties). Additional time-varying covariates were considered, including hours since last alcohol drink and day of the week (weekday [Monday – Thursday]) vs. weekend [Friday – Sunday]), and were only included in final models if they were significant predictors in the model at $p < 0.10$. Exploratory analyses examined each individual EACS item as the outcome (dichotomous) to explore the relationship between alcohol use and domain-specific cognitive difficulties.

Hypothesis 2b. Greater depressed mood will be related to higher likelihood of concurrent cognitive difficulties. As in Hypothesis 2a, mixed-effects logistic regression models were used to analyze these data. Again, the outcome variable was dichotomous cognitive difficulties. The primary predictor variable was level of depressed mood, as assessed by the EMA survey item asking participants to rate how depressed they currently feel on a likert-type scale from 0=*Not at all* to 4=*Very much*. This variable was person-mean centered in order to understand how fluctuations in depressed mood (relative to one's average level of depressed mood) relate to cognitive difficulties. We examined whether level of depressed mood predicted cognitive difficulties within the same EMA survey, covarying for average depressed mood (i.e., a participant's average depressed mood rating over the 14-day EMA monitoring period), time of

day, study day, age, and objective neurocognitive impairment. Exploratory analyses examined each individual EACS item as the outcome (dichotomous) to explore the relationship between depressed mood and domain-specific cognitive difficulties.

Hypothesis 2c. Engagement in cognitively demanding activities will be related to higher likelihood of concurrent cognitive difficulties only in the context of objective neurocognitive impairment. Consistent with Hypotheses 2a and 2b, the outcome variable for Hypothesis 2c was dichotomous cognitive difficulties. The primary predictor variables were dichotomous engagement in cognitively demanding activities, objective neurocognitive impairment, and an interaction between the two. Engagement in cognitively demanding activities was assessed by an EMA survey item asking participants to report whether they had engaged in any cognitively demanding activities since the last survey by selecting all applicable activities from a comprehensive list (adapted from a newly developed measure piloted at the HNRP; (Paolillo, Hussain, Moore, Moore, & Heaton, 2019). Each list item had been previously identified as cognitively demanding (e.g., paying bills, attempting a new task). Participants could select "Other" if they engaged in a cognitively demanding activity not on the list and had an opportunity to write the activity in a text box. Participants were able to select "None" when they had not engaged in any cognitively demanding activities. Mixed-effects logistic regression models were used to analyze these data and examine the cross-level interaction between engagement in cognitively demanding activities (within-person; time-varying) and neurocognitive impairment (between-person; time-invariant), covarying for proportion of surveys with reported engagement in cognitively demanding activities, age, time of day, and study day. Examination of this interaction will determine whether engagement in cognitively demanding activities related to cognitive difficulties *only* among participants who are

neurocognitively impaired. If the interaction is not significant, it will be removed from the model to examine the main effect of cognitively demanding activities on cognitive difficulties. Exploratory analyses examined each individual EACS item as the outcome (dichotomous) to explore the relationship between cognitively demanding activities and domain-specific cognitive difficulties.

Exploratory Aim. Examine acceptability, feasibility, and validity of an objective measure of alcohol use during the EMA monitoring period (i.e., a portable alcohol breathalyzer). To evaluate acceptability of the portable alcohol breathalyzer, we used descriptive statistics to summarize data from the post-study feedback questionnaire on which participants rated their experience using the breathalyzer. Feasibility was examined by calculating the proportion of times a participant used the breathalyzer out their total number of completed EMA surveys (i.e., breathalyzer adherence). We evaluated validity of the breathalyzer by examining the within-person relationship between breathalyzer-measured BAC values and reported number of alcohol drinks on the same EMA survey using linear mixed-effects modeling.

All statistical analyses were performed using R version 3.5.0. The "lme4" package was used to conduct all mixed-effects regressions (D. Bates, Mächler, Bolker, & Walker, 2014).

2.7 Handling Missing Data

One advantage of EMA is that a large amount of repeated measures data is collected over time, so mixed-effects regressions can be used to model outcomes while including participants with missing data, without relying on data imputation procedures. EMA data were included for all participants completing at least 30% of programmed EMA assessments (guaranteeing the equivalent of at least four full days of data); this criterion was met for all 23 participants. This

criterion for minimum compliance is justified to permit analyses of both within- and across-day variance (Stone & Shiffman, 2002). To ensure that missing data was not related to participant characteristics, we also examined the relationship between EMA adherence (i.e., proportion of surveys completed out of 56 possible surveys) and demographics, mood, and neurocognition.

3. RESULTS

3.1 Participant Characteristics

Demographic and clinical characteristics are displayed in Table 2. Data regarding HIV disease characteristics and DSM-IV psychiatric and substance use diagnoses were linked from participants' previous parent study visit at the HNRP, which was no more than two years prior to the current baseline visit (median days since parent study visit = 245, range = 0 – 728). All other data represents that which was collected at the current baseline visit. On average, our participants were in their mid-50s [range = 47-72], predominantly non-Latinx White, male, with about 14 years of education. Only 13% had current major depressive disorder (MDD) and the entire sample's average BDI-II score was in the minimal range. A majority of participants (61%), however, had a lifetime history of MDD. Notably, our sample also reported moderate symptoms of anxiety on average.

In terms of alcohol use characteristics, about one-fifth of our participants met criteria for a current alcohol use disorder and all of them had a lifetime history of alcohol use disorder. Participants' average AUDIT score fell within the range indicating moderate-to-severe current alcohol use (mean = 15.5, range = 4 – 36). The average total number of drinks that participants reported during the 14-day EMA monitoring period was about 55 drinks (range = 16 – 120), with about 3 drinks consumed per drinking occasion (range = 1 – 15) and an average BAC of 0.08 per drinking occasion (range = 0.00 – 0.22; as measured by the portable alcohol breathalyzer on surveys when they reported concurrent alcohol use). Notably, when examining reported alcohol consumption over the 14-day EMA monitoring period, linear mixed-effects regression showed a within-person effect of study day such that participants reported fewer drinks consumed over time (b = -0.028, SE = 0.014, p = 0.039). Consistent with participant inclusion/exclusion criteria,

no participants met criteria for a current non-alcohol substance use disorder. Only about 30% had a lifetime history of other substance use disorder.

Participants had been living with HIV for an average of about 20 years (range = 6 – 34) and over half had a history of AIDS. Participants' HIV disease was relatively well-controlled, with a median CD4 count in the high 400s, all but one participant on ART, and only two participants with detectable plasma viral load. With regard to neurocognitive functioning, 6 (26%) participants were neurocognitively impaired, with group mean NIH Toolbox Fluid Cognition T-score and Crystallized Cognition T-score both in the average range. The majority of participants (74%) were also unemployed; however, less than half of participants (43%) were dependent in IADLs. Additionally, 35% of participants endorsed cognitive difficulties on the EACS screening questions and the median PAOFI score was 1.5 (range = 0 – 24). During the 14-day EMA monitoring period, participants reported having cognitive difficulties on a median of 8% of surveys with a range of 2% to 96%, indicating that all participants had at least some variability in their report of cognitive difficulties (i.e., no one denied having cognitive difficulties on all surveys and vice versa).

Table 2. Demographic and clinical characteristics (N = 23)

	Mean (SD), Median [IQR], or n (%)
Demographics	
Age (years)	56.9 (6.1)
Education (years)	14.5 (2.4)
Sex (% male)	22 (96%)
Race/Ethnicity	
Non-Latinx White	14 (61%)
Latinx	7 (30%)
Black	2 (9%)

Table 2, continued

	Mean (SD), Median [IQR], or n (%)
Psychiatric Characteristics	
Current Major Depressive Disorder	3 (13%)
Lifetime Major Depressive Disorder	14 (61%)
Beck Depression Inventory-II score	11.8 (7.2)
Beck Anxiety Inventory	28.3 (8.6)
Alcohol and Substance Use Characteristics	
Current alcohol use disorder	5 (22%)
Lifetime alcohol use disorder	23 (100%)
AUDIT Score	15.5 (9.7)
Current other substance use disorder	0 (0%)
Lifetime other substance use disorder	7 (30%)
EMA-Reported Alcohol Use	
Total number of drinks during EMA period	55.2 (27.8)
Number of drinks on each drinking occasion	2.9 (2.0)
BAC on each drinking occasion (gram%)	0.08 (0.04)
HIV Disease Characteristics	
Estimated years living with HIV	20.6 (8.7)
History of AIDS	13 (57%)
Nadir CD4 (cells/µl)	100 [34 – 405]
Current CD4 (cells/µl)	476 [322 – 657]
Plasma viral load detectable (>50 copies/mL)	2 (9%)
On ART	22 (96%)
Neurocognitive Functioning	
NIH Toolbox Cognition Battery	
Fluid GDS Impairment (impaired)	6 (26%)
Fluid Cognition T-Score	49.2 (10.1)
Crystallized Cognition T-Score	53.6 (8.8)
Everyday Functioning	
Employment (% unemployed)	17 (74%)
IADL Dependence (% dependent)	10 (43%)
Cognitive Difficulties	
In-person EACS Screening Questions	8 (35%)
Proportion of EMA surveys with reported cognitive difficulties	0.08 [0.02 – 0.27]
PAOFI Score	1.5 [0.25 – 5.75]

Note. AUDIT = Alcohol Use Disorders Identification Test; BAC = blood alcohol content (measured via portable alcohol breathalyzer); AIDS = Acquired Immunodeficiency Syndrome; ART = Antiretroviral Therapy; NIH = National Institutes of Health; GDS = Global Deficit Score; IADL = Instrumental Activities of Daily Living; EACS = European AIDS Clinical Society; PAOFI = Patient's Assessment of Own functioning Inventory; specific substances that were assessed in the diagnosis of "other" substance use disorders included cannabis, cocaine, methamphetamine, opioids, sedatives, phencyclidine (PCP), hallucinogens, and inhalants.

3.2 EMA Adherence

Regarding EMA usage and adherence, participants completed an average of 83% of all possible surveys (SD = 15%; range = 39% to 100%). This resulted in 1071 completed EMA surveys across the 23 participants. EMA adherence (i.e., proportion of completed EMA surveys) was not related to age (r = 0.07, p = 0.77), years of education (r = 0.22, p = 0.32), total number of drinks reported during the EMA study period (r = -0.07, p = 0.77), BDI-II score (r = 0.05, p = 0.84), BAI score (r = 0.01, p = 0.95), neurocognitive impairment status (impaired: mean = 81%, SD = 23%; normal: mean = 84%, SD = 12%; $t(21)$ = 0.46, p = 0.65), or phone type (personal phone [n=18]: mean = 85%, SD = 13%; study phone [n=5]: mean = 75%, SD = 22%, p = 0.22). Although EMA adherence did not relate to these demographic or neuropsychiatric factors, mixed-effect logistic regression showed a within-person effect of study day, such that participants were increasingly less likely to complete their EMA surveys as the 14-day EMA monitoring period progressed (OR = 0.894 [per 1 day increase in study day], 95%CI = 0.858 – 0.931, $p < 0.001$).

3.3 Convergent Validity of EMA Self-Reported Cognitive Difficulties and Neurocognitive Functioning

The proportion of surveys on which participants reported any cognitive difficulties was negatively associated with Fluid Cognition T-score (b = -13.06, SE = 7.10, p = 0.040). Logistic regression, however, showed that the proportion of surveys on which participants reported cognitive difficulties did not significantly predict neurocognitive impairment status (OR = 8.32 [per increase in predictor over entire range], 95%CI = 0.35 – 336.49, p = 0.100). Although this did not reach statistical significance likely due to limited sample size, the estimated odds ratio

indicates that participants with the most cognitive difficulties were about eight times more likely to be neurocognitively impaired compared to those with the fewest cognitive difficulties. When examining each EACS item individually, higher proportions of reported memory difficulties (b = -22.59, SE = 10.59, p = 0.022) and slowed thinking (b = -24.20, SE = 8.61, p = 0.005) were significantly related to worse Fluid Cognition T-score; however, the proportion of surveys on which participants reported attention difficulties was only marginally related to worse Fluid Cognition T-score (b = -10.94, SE = 7.41, p = 0.076). Individual EACS items were not related to neurocognitive impairment status (ps > 0.05).

3.4 Sensitivity and Specificity to Detect Neurocognitive Impairment

The standard in-person EACS screening questions were 67% sensitive and 76% specific in identifying objective neurocognitive impairment (OR = 6.5, 95%CI = 0.85 – 49.69, p = 0.08). The ROC analysis examining predictive ability of the EMA-administered EACS questions (i.e., the proportion of surveys on which participants reported cognitive difficulties) identified 0.089 as an optimal cut-point to detect neurocognitive impairment (AUC = 0.78), with 100% sensitivity and 65% specificity (**Figure 5**). In other words, individuals who reported cognitive difficulties on about 9% of surveys or more were identified as having high risk for objective neurocognitive impairment. The McNemar's chi-squared tests demonstrated that the two administration methods of the EACS screening questions did not significantly differ in sensitivity ($\chi2(1, N = 23) = 0.50$, p = 0.480) nor specificity ($\chi2(1, N = 23) = 0.25$, p = 0.617) to detect objective neurocognitive impairment. The two different EACS administration methods had 74% agreement (i.e., they classified 17 participants identically in terms of their risk for neurocognitive impairment).

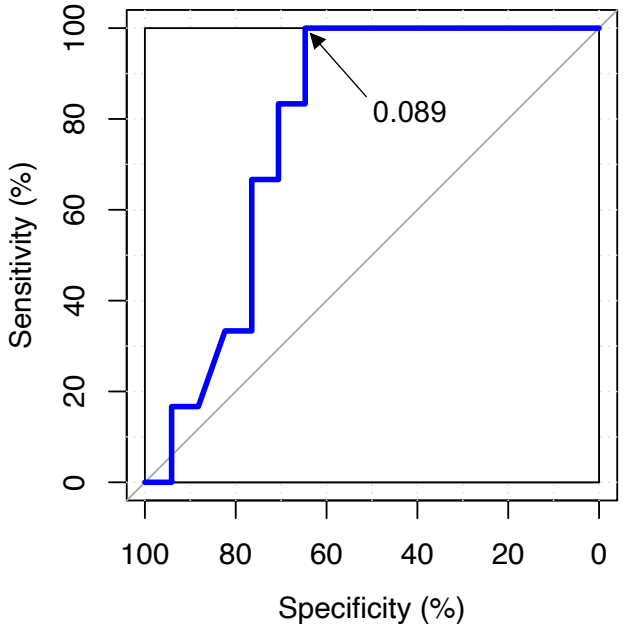

Figure 5. ROC curve identifying 0.089 as the optimal proportion of EMA surveys with reported cognitive difficulties to detect objective neurocognitive impairment.

3.5 Post-hoc Analyses for Hypotheses 1a and 1b

Using demographic- and reading-corrected NIH Toolbox Cognition scores as our measure of cognitive functioning, the entire sample had a mean Fluid Cognition T score of 47.2 (SD = 9.8) and 8 (35%) were neurocognitively impaired (Fluid GDS ≥ 0.5). Regarding convergent validity (Hypothesis 1a), the proportion of EMA surveys on which participants reported any cognitive difficulties was negatively associated with the demographic- and reading-corrected Fluid Cognition T score (b = -12.66, SE = 6.93, p = 0.041). The relationship between neurocognitive impairment and the demographic- and reading-corrected Fluid Cognition T score was marginally significant *(OR* = 1.24 [per 0.10 change in predictor], 95%CI = 0.92 – 1.85, p = 0.095). Regarding discriminative validity (Hypothesis 1b), the in-person EACS was 63% sensitive and 83% specific in identifying neurocognitive impairment. The ROC analysis examining predictive ability of the EMA-administered EACS questions (i.e., the proportion of

surveys on which participants reported cognitive difficulties) still identified 0.089 as an optimal cut-point to detect neurocognitive impairment (AUC = 0.76), with 88% sensitivity and 77% specificity. The McNemar's chi-squared tests showed that the two administration methods of the EACS screening questions did not significantly differ in sensitivity nor specificity (*p*s > 0.05) to detect objective neurocognitive impairment.

Using participants' first-ever NIH Toolbox Cognition scores (i.e., from their first NIH Toolbox assessment at the HNRP), the entire sample had a mean Fluid Cognition T score of 48.3 (SD = 11.7) and 9 (39%) were neurocognitively impaired (Fluid GDS ≥ 0.5). Participants' first-ever Toolbox Cognition assessment was 1.3 years prior to the current study on average (SD = 1.9; range = 0-5 years). Regarding convergent validity (Hypothesis 1a), the proportion of EMA surveys on which participants reported any cognitive difficulties was significantly associated with participants' first-ever Fluid Cognition T score (b = -20.14, SE = 7.73, p = 0.008) and neurocognitive impairment status (OR = 2.13 [per 0.10 change in predictor], 95%CI = 1.22 – 5.35, p = 0.022). Regarding discriminative validity (Hypothesis 1b), the in-person EACS was 67% sensitive and 86% specific in identifying neurocognitive impairment. The ROC analysis examining predictive ability of the EMA-administered EACS questions (i.e., the proportion of surveys on which participants reported cognitive difficulties) still identified 0.089 as an optimal cut-point to detect neurocognitive impairment (AUC = 0.90), with 100% sensitivity and 79% specificity. The McNemar's chi-squared tests showed that the two administration methods of the EACS screening questions did not significantly differ in sensitivity nor specificity (*p*s > 0.05) to detect objective neurocognitive impairment.

3.6 Real-Time Predictors of Cognitive Difficulties

Alcohol use. When examining the concurrent relationship between alcohol use and cognitive difficulties, the final mixed-effects logistic regression model (i.e., covarying for average alcohol consumption, time of day, age, neurocognitive impairment status, and study day) revealed that number of drinks consumed was significantly related to likelihood of endorsing cognitive difficulties on the same survey within persons (OR = 1.372 [per 1 drink increase], 95%CI = 1.218 – 1.545, $p < 0.001$; **Table 3**). The direction of this relationship indicates that participants were more likely to report cognitive difficulties on surveys when they drank more than their average amount of alcohol (**Figure 6**). Examination of the lagged relationship, however, showed that number of drinks consumed did not significantly predict likelihood of endorsing cognitive difficulties on the *next* survey (OR = 1.041, 95%CI = 0.865 – 1.25, $p = 0.669$). When examining the EACS items individually, results demonstrated that a greater number of drinks was associated with higher likelihood of endorsing each of the three items on the same survey within persons, including memory problems (OR = 1.211, 95%CI = 1.033 – 1.420, $p = 0.018$), slowed thinking (OR = 1.333, 95%CI = 1.158 – 1.535, $p < 0.001$), and attention problems (OR = 1.460, 95%CI = 1.271 – 1.678, $p < 0.001$).

Table 3. Mixed-effects logistic regression results examining the concurrent relationship between alcohol use and likelihood of endorsing cognitive difficulties

	Logit	OR	95% CI	*p*-value
Within-person level				
Number of alcohol drinks (person-mean centered)	0.316	1.372	1.218 – 1.545	**<0.001**
Time of day	-0.175	0.840	0.693 – 1.017	0.074
Study day	-0.059	0.943	0.894 – 0.994	**0.030**
Between-person level				
Average alcohol consumption	-0.549	0.578	0.188 – 1.776	0.338
Age	-0.039	0.962	0.777 – 1.191	0.723
Neurocognitive impairment (ref: no)	2.543	12.715	0.828 – 195.200	0.068

Note. Bolded *p*-values are significant at $p < 0.05$.

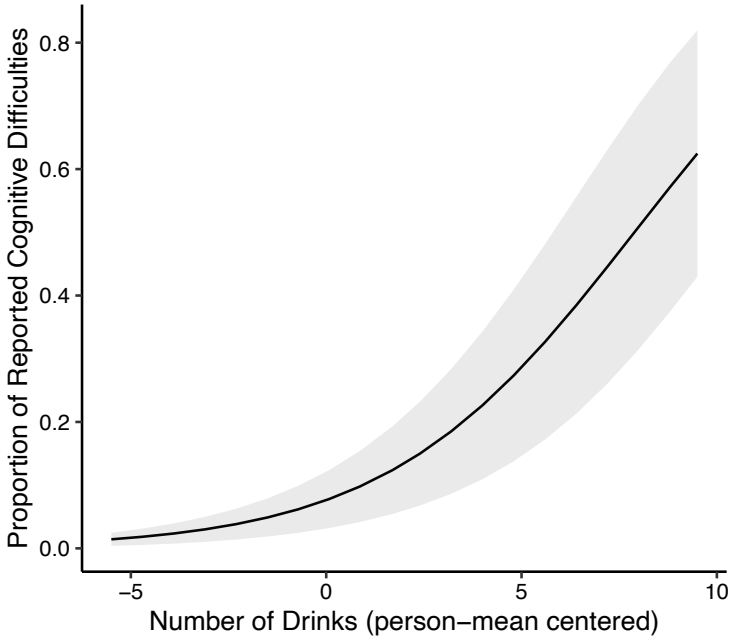

Figure 6. Concurrent relationship between number of alcohol drinks and likelihood of reporting cognitive difficulties on the same EMA survey within persons.

Depressed mood. Mixed-effects logistic regression revealed a significant relationship between depressed mood and likelihood of endorsing cognitive difficulties on the same survey within persons (OR = 1.802 [per 1 unit increase in depressed mood rating], 95%CI = 1.115 – 2.910, $p = 0.016$; **Table 4**). The direction of this relationship indicates that participants were more likely to report cognitive difficulties when they rated higher depressed mood than usual (i.e., compared to their average level of depressed mood; **Figure 7**). When examining the EACS items individually, results demonstrated that a higher depressed mood rating was associated with higher likelihood of endorsing slowed thinking (OR = 2.768, 95%CI = 1.570 – 4.881, $p < 0.001$) and attention problems (OR = 1.874, 95%CI = 1.087 – 3.232, $p = 0.024$), but not memory problems (OR = 1.534, 95%CI = 0.841 – 2.798, $p = 0.163$).

Table 4. Mixed-effects logistic regression results examining the concurrent relationship between depressed mood and likelihood of endorsing cognitive difficulties

	Logit	OR	95% CI	*p*-value
Within-person level				
Depressed mood (person-mean centered)	0.559	1.802	1.115 – 2.910	**<0.061**
Time of day	-0.0.029	0.971	0.807 – 1.168	0.755
Study day	-0.053	0.948	0.899 – 1.000	0.050
Between-person level				
Average depressed mood	1.427	4.165	0.193 – 9.008	0.363
Age	-0.050	0.951	0.767 – 1.178	0.645
Neurocognitive impairment (ref: no)	2.248	9.469	0.634 – 141.500	0.103

Note. Bolded p-values are significant at $p < 0.05$.

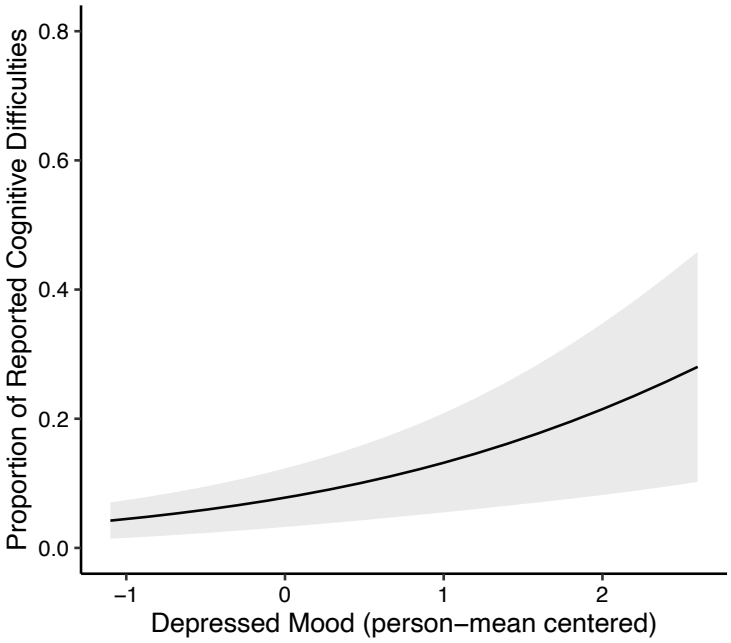

Figure 7. Concurrent relationship between depressed mood and likelihood of reporting cognitive difficulties on the same EMA survey within persons.

Cognitively demanding activities. Results showed that the within-person relationship between doing a cognitively demanding activity and reporting cognitive difficulties was not moderated by neurocognitive impairment status (cross-level interaction: logit = 0.179, SE = 0.498, $p = 0.719$; **Table 5**). After removing the cross-level interaction from the model, there was also no significant within-person main effect of doing a cognitively demanding activity (OR = 0.791, 95%CI = 0.503 – 1.242, $p = 0.307$). When examining the EACS items individually, however, results demonstrated a significant within-person main effect of doing a cognitively demanding activity on the likelihood of endorsing attention problems (OR = 0.537, 95%CI = 0.312 – 0.923, $p = 0.025$). The direction of this relationship indicates that doing a cognitively demanding activity was associated with a lower likelihood of reporting attention problems

(**Figure 8**). Cognitively demanding activities did not predict the likelihood of reporting memory problems (OR = 0.638, 95%CI = 0.355 – 1.147, $p = 0.134$) or slowed thinking (OR = 0.699, 95%CI = 0.423 – 1.158, $p = 0.165$).

Table 5. Mixed-effects logistic regression results examining whether the concurrent relationship between engagement in cognitively demanding activities and likelihood of endorsing cognitive difficulties differs by neurocognitive impairment status (i.e., the cross-level interaction)

	Logit	OR	95% CI	*p*-value
Within-person level				
Cognitively demanding activity (ref: no)	-0.296	0.744	0.421 – 1.314	0.308
Time of day	-0.045	0.956	0.796 – 1.147	0.626
Study day	-0.063	0.939	0.891 – 0.990	**0.020**
Between-person level				
Proportion of surveys with reported cognitively demanding activities	1.821	6.178	0.026 – 149.400	0.516
Age	-0.031	0.969	0.786 – 1.195	0.769
Neurocognitive impairment (ref: no)	2.042	7.706	0.450 – 13.210	0.159
Cross-level interaction				
Cognitively demanding activity * Neurocognitive impairment	0.179	--	--	0.719

Note. Bolded p-values are significant at $p < 0.05$.

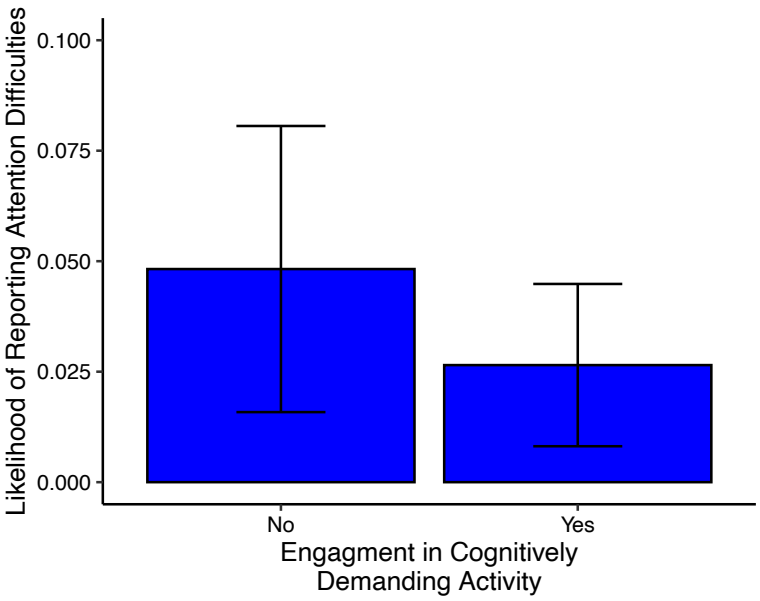

Figure 8. Concurrent relationship between doing a cognitively demanding activity and likelihood of reporting cognitive difficulties on the same EMA survey within persons.

3.7 Portable Alcohol Breathalyzer Use

Acceptability. All 23 participants completed the post-study feedback questionnaire at their follow-up visit. On an item asking participants to rate "How challenging was it for you to use the breathalyzer?" on a scale from 1 (Not at all) to 10 (Very much), the median score was 0 (IQR = 0 - 2.5) with a range from 0 to 8. The following five items regarding breathalyzer use had response options ranging from 0 (Not at all) to 4 (Very much). In response to the item stating, "The device interfered with my activities," participants had a median rating of 0 (range 0-2). Participants seemed to "somewhat" enjoy using the breathalyzer, as their average rating in response to the item stating, "I enjoyed the experience," was about 2.24 (SD = 1.2; range = 0-4). Participants also found the breathalyzer "somewhat" to "quite a bit" helpful, with an average rating of 2.65 (SD = 1.17; range = 0-4) in response to "A device like this could be helpful to me in the future," and an average rating of 2.41 (SD = 1.37; range = 0-4) in response to "The device made me pay attention to things I normally wouldn't have paid attention to." Finally, participants

seemed somewhat willing to use the breathalyzer in the future, with an average rating of 2.88 (SD = 1.11; range = 0-4) in response to "I would like to use this device again."

Feasibility. Out of each participant's total completed EMA surveys, they concurrently used the breathalyzer a median of 98% of the time (IQR = 91% – 100%; range = 19% – 100%), yielding 967 total BAC data points. Similar to participants' adherence to EMA surveys in general, there was a within-person effect of study day on breathalyzer adherence, such that participants were increasingly less likely to use the breathalyzer upon completion of the EMA survey as the study progressed (b = -0.125, SE = 0.040, p = 0.002). On the post-study feedback questionnaire, participants were also given an opportunity to write in reasons why they may have not used the breathalyzer during survey completion. Three participants reported that they had sometimes forgotten to bring the breathalyzer with them; three participants reported that their difficulty using the breathalyzer sometimes prevented them from obtaining a BAC estimate; one participant reported that the battery died near the end of the study period; and one participant reported that they did not want to use the breathalyzer while "in public."

Validity. Results of the linear mixed-effect regression showed that the reported number of alcohol drinks consumed was significantly associated with the BAC estimate from the portable breathalyzer on the same survey (b = 0.015, SE = 0.0005, $p < 0.001$). The direction of this relationship indicates that for each additional drink consumed, estimated BAC increased by about 0.015 gram% within persons (**Figure 9**). Although this bivariate relationship was strong and statistically significant, there appeared to be noticeable heterogeneity (e.g., a number of cases had BAC estimates of 0 despite reporting concurrent alcohol consumption). Thus, further examination revealed a significant within-person interaction between number of drinks and hours

since last drink (b = -0.002, SE = 0.0006, p = 0.001) such that the relationship between number of drinks and BAC was strongest when alcohol consumption was more recent (**Figure 10**).

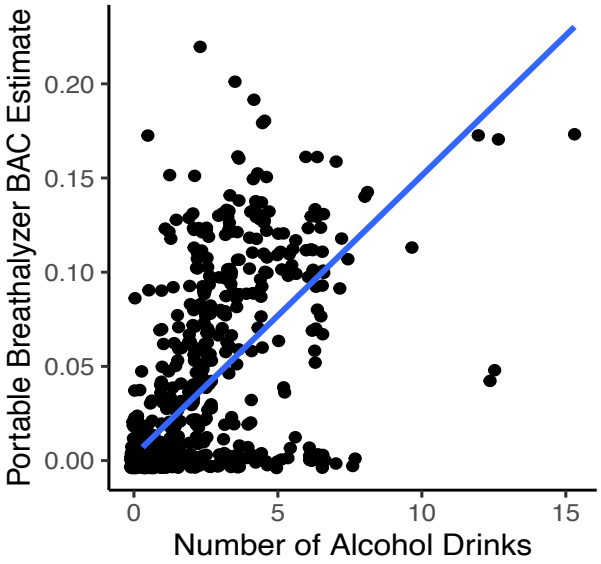

Figure 9. Within-person relationship between number of alcohol drinks consumed and estimated blood alcohol content (BAC) at the same timepoint.

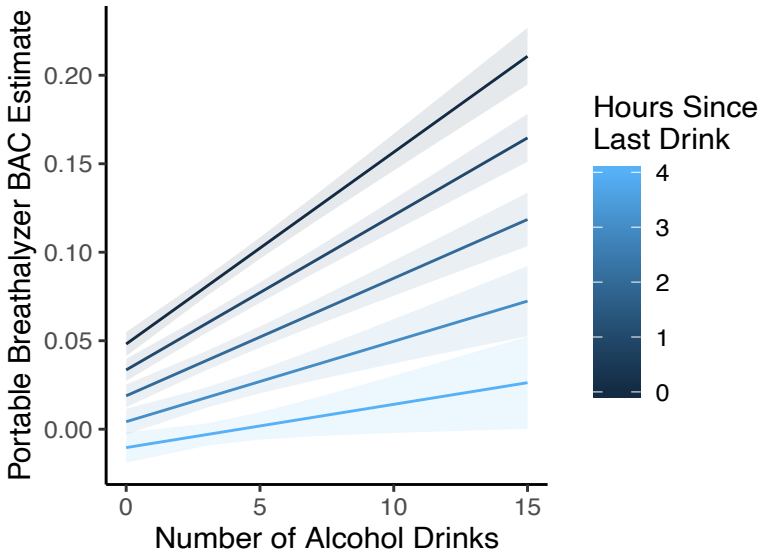

Figure 10. The within-person relationship between self-reported number of alcohol drinks consumed and breathalyzer-estimated blood alcohol content (BAC) depends on recency of alcohol consumption.

3.8 Overall Study Feedback

On the post-study feedback questionnaire, participants were asked about different aspects of their experience participating in the study. When asked about challenges they experienced during the study, 12 (52%) reported that they had no challenges, four participants reported difficulty remembering to bring the phone or breathalyzer with them, four participants reported being unable to take the phone or breathalyzer with them to certain places, two reported having trouble fitting the phone and/or breathalyzer in their pocket or bag, and one reported difficulty hearing the text message alerts with the request to take the EMA surveys. On average, participants reported that it was not very challenging to answer the survey questions, with a median score of 0 (IQR = 0 – 1; range = 0 – 7) on a scale from 0 (Not at all) to 10 (Very much). Participants also reported that the smartphone and EMA surveys did not much interfere with their activities, with a median score of 0 (IQR = 0 – 0.5; range = 0 – 2) on a scale from 0 (Not at all) to 4 (Very much). Finally, most participants reported enjoying their study experience, with a median rating of 3 (IQR = 1.5 – 4; range = 0 – 4) on a scale from 0 (Not at all) to 4 (Very much).

4. DISCUSSION

This study examined the use of an innovative assessment methodology to better capture real-world functional deficits in the context of HIV, heavy alcohol use, and neurocognitive impairment. This is one of the first studies to our knowledge to explore whether repeated self-report assessment of cognitive difficulties in real-time and in real-world settings via EMA would reduce self-report bias and improve accuracy of individuals' reported experiences as it relates to objective neurocognitive deficits. In addition, this is the only study to our knowledge that has examined real-time temporal predictors of cognitive difficulties; predictors considered included alcohol use, mood, and engagement in cognitively demanding activities. These findings enhance our understanding of other factors that influence subjective perception of one's own functioning beyond objective neurocognition. Finally, our study also importantly explored the acceptability, feasibility, and validity of an objective measure of alcohol use (i.e., a portable alcohol breathalyzer) as a potentially more accurate way to monitor alcohol consumption over time among PWH who drink heavily.

4.1 Evaluation of EMA-Administered EACS Screening Questions

The first aim of this study was to evaluate the psychometric properties of the EMA-administered EACS screening questions, specifically as it related to convergent and criterion validity. We hypothesized not only that the EMA-administered EACS screening questions would be significantly related to objective, in-laboratory neurocognitive performance, but also that the EACS questions repeatedly administered via EMA would be more sensitive and specific to identify individuals with objective neurocognitive impairment compared to that of the standard, in-person EACS screening questions. Partially consistent with our first hypothesis, we found that

the proportion of EMA surveys on which participants reported any cognitive difficulties was significantly related to Fluid Cognition T score. Although the relationship with neurocognitive impairment status was not statistically significant in the primary analyses, the relationship was strong with an odds ratio indicating that participants with the most cognitive difficulties were about 8 times more likely to be neurocognitively impaired than those with the least cognitive difficulties. Thus, the lack of statistical significance was likely related to issues of statistical power. In our sample of 23 participants, only six were identified as having objective neurocognitive impairment based on our in-person neurocognitive testing in the primary analyses. This greatly limited our statistical power to identify differences between neurocognitive impairment status groups. Nevertheless, even with the current, small participant sample, statistical power was adequate when using a continuous outcome measure of cognitive functioning, as power to detect relationships among continuous variables is greater than that of dichotomous variables (Altman & Royston, 2006).

It is also possible that self-reported cognitive difficulties may be more sensitive to subtle, mild declines in objective neurocognition that do not necessarily reach the level of diagnostic neurocognitive impairment. For example, among older adult populations susceptible to age-related neurodegenerative diseases (e.g., Alzheimer's disease), studies have proposed that subjective cognitive decline may be an early marker of brain dysfunction that is too subtle to be detected by objective performance on neurocognitive tests (Amariglio et al., 2012; Jessen et al., 2014; Slot et al., 2019). Conversely, other studies have suggested that the insight and awareness needed to prompt an individual to self-report cognitive difficulties (even in real-time) is reduced after neurocognition declines past the threshold at which a neurocognitive disorder would be diagnosed (Fragkiadaki et al., 2016; Zanetti et al., 1999). Thus, we may have found an

association between cognitive difficulties and a continuous measure of neurocognitive functioning due to the possibility that the relationship is strongest at the higher range of neurocognitive performance (i.e., above the level of impairment). This would have significant clinical implications for possible early detection of neurocognitive decline. Future studies with larger sample sizes may benefit from examining a possible quadratic association between self-reported cognitive difficulties and objective neurocognition to clarify this relationship.

Inconsistent with our second hypothesis, the EMA-administered EACS questions were not significantly more sensitive or specific in identifying neurocognitive impairment compared to that of the standard EACS administration. Again, however, we were likely underpowered to be able to detect a statistical difference in sensitivities and specificities by EACS administration method. The standard in-person EACS questions had low sensitivity as well as specificity (i.e., 67% and 76%, respectively) to detect neurocognitive impairment in our sample, and the low sensitivity is especially limiting for a screening measure. This is somewhat consistent with the literature on the EACS screening questions, which suggests that these items better identify symptomatic HAND as opposed to any neurocognitive impairment (i.e., including asymptomatic; (Metral et al., 2020). In contrast, our EMA-administered EACS items were highly sensitive (100%), but had modest specificity (65%). The low specificity of the EMA-administered EACS questions reflects the fact that several participants *without* objective neurocognitive impairment had a high proportion of surveys with reported cognitive difficulties (i.e., ≥ 9% of surveys). This low specificity is likely to be at least partly related to the factors found to be real-time predictors of cognitive difficulties in the second study aim (e.g., concurrent alcohol use). Although the goal of our repeated assessment of cognitive difficulties was to improve ecological validity and reduce self-report response bias, there still appears to be many

other factors that contribute to an individual's experience of cognitive difficulties that are unrelated to objective neurocognitive impairment status. The 100% sensitivity of the EMA-administered EACS questions, however, is notable. This indicates that, using the identified cutoff, our EMA-administered EACS questions correctly identified 100% of the participants with neurocognitive impairment. Despite the moderate rate of false positives leading to relatively low specificity, this methodology may still have clinical utility above that of the standard EACS questions if a clinic's / clinician's goal is to be more inclusive in identifying individuals with potential neurocognitive impairment and greater healthcare needs.

Finally, it is important to mention that the post-hoc analyses showed somewhat higher rates of neurocognitive impairment when using alternative NIH Toolbox Cognition metrics (i.e., demographic- and reading-corrected scores and first-ever NIH Toolbox Cognition scores). These higher rates are more consistent with rates of neurocognitive impairment among PWH in the wider literature (Heaton et al., 2010) and appeared to be more strongly related to the EMA-administered EACS questions. Future research is needed to both support our findings with a larger sample size as well as with additional measures of objective cognitive functioning.

4.2 Examining Real-Time Predictors of Cognitive Difficulties

The second primary aim of this study was to examine specific factors that related to experience of cognitive difficulties in real-time. We first hypothesized that both greater alcohol use and higher levels of depressed mood would be associated with a greater likelihood of reporting cognitive difficulties at the same timepoint. We also hypothesized that engagement in a cognitively demanding activity would relate to higher likelihood of experiencing cognitive difficulties only among those with objective neurocognitive impairment. Consistent with the first

hypotheses, we found that: 1) on occasions when participants drank alcohol more than their average amount, they were significantly more likely to report cognitive difficulties; and 2) on occasions when participants reported being more depressed than their average level, they were significantly more likely to report cognitive difficulties. Interestingly, examination of the EACS items individually showed that alcohol use was related to higher likelihood of reporting difficulties with all three domains assessed (i.e., memory, slowed thinking, and attention), whereas depressed mood was only related to a higher likelihood of reported slowed thinking and attention difficulties. This may point towards a distinction between the acute behavioral presentations associated with drinking alcohol versus being depressed. Inconsistent with our last hypothesis, however, we found that doing a cognitively demanding activity was related to a *lower* likelihood of reporting cognitive difficulties (i.e., specifically attention difficulties only), and that this did not differ by neurocognitive impairment status.

To our knowledge, this is the first study to date to show that alcohol use acutely relates to the subjective experience of cognitive difficulties within persons. There have been in-laboratory cross-sectional studies examining differences in metacognition (i.e., knowledge and awareness about one's own cognitive abilities) between chronic heavy alcohol users and non-users, with results suggesting that alcohol users typically have less accurate perceptions about their objective functioning (i.e., they overestimate their abilities) compared to non-users (Le Berre et al., 2016; Le Berre et al., 2010; Le Berre & Sullivan, 2016). Our current within-person finding, however, suggests that even among a clinical population with less accurate metacognition overall (compared to non-drinkers), they are still likely to perceive *changes* in their cognitive functioning in the context of increased alcohol use. This is consistent with what is known regarding the acute neurobehavioral effects of alcohol consumption. For example, acute alcohol

intoxication is known to disrupt a wide range of cognitive functions, including memory, executive functioning (e.g., planning, inhibition, impulse control, error-monitoring), attention, working memory, processing speed, and motor control (Boissoneault, Sklar, Prather, & Nixon, 2014; Peterson, Rothfleisch, Zelazo, & Pihl, 1990; Schweizer et al., 2006; Tiplady, Oshinowo, Thomson, & Drummond, 2009; Van Skike, Goodlett, & Matthews, 2019). Despite deficits in insight and error-monitoring that typically accompany both chronic alcohol use and acute alcohol intoxication, our participants appeared to be aware of cognitive difficulties experienced when they drank more alcohol than usual. We also hypothesized that alcohol use reported at one timepoint would relate to greater likelihood of reporting cognitive difficulties at the next timepoint as well; however, our findings did not support this hypothesis. Instead, the *concurrent* relationship among alcohol use and cognitive difficulties suggests that these factors influence each other within persons only transiently. Notably, there was also no between-person effect of average alcohol consumption, indicating that the proportion of surveys on which participants reported cognitive difficulties did not differ by participants' average level of alcohol consumption during the 14-day EMA monitoring period. Consistent with the previously described research on metacognition (Le Berre et al., 2016; Le Berre et al., 2010; Le Berre & Sullivan, 2016), this result demonstrates that individuals who drink more would not be more likely to report more cognitive difficulties on average. Instead, our findings highlight the within-person, concurrent, and transient nature of the observed relationship between alcohol use and self-reported cognitive difficulties.

Our finding demonstrating the within-person relationship between depressed mood and concurrent subjective cognitive difficulties supports previous research in this area. For example, several longitudinal studies have demonstrated that depressive symptoms and subjective

cognitive difficulties fluctuate in tandem within persons over time, and that this is consistent across populations (Donnelly, Donnelly, Warner, Kittleson, & King, 2018; Hülür, Hertzog, Pearman, Ram, & Gerstorf, 2014; Paolillo et al., June 2019). The mechanisms underlying this relationship are likely multifaceted. First, negative self-appraisal is a characteristic feature of depression (Beck, 2002; Davey, Breakspear, Pujol, & Harrison, 2017), which is likely to include negative and often inaccurate perceptions about one's own cognitive functioning in daily life. In addition, however, acute increases in depressive symptoms have also shown to be related to transient decreases in objective neurocognitive performance in both PWH and people without HIV (Brose, Schmiedek, Lovden, & Lindenberger, 2012; Hülür et al., 2014; Laukka, Dykiert, Allerhand, Starr, & Deary, 2018; Paolillo et al., 2020). These objective decreases in neurocognition may be accurately perceived by individuals, leading to more subjective cognitive difficulties. Notably, these transient decreases in neurocognition are often driven by slowed processing speed (a core feature of the behavioral presentation of clinical depression; (American Psychiatric Association, 2013; Paolillo et al., 2020), which is consistent with the specific EACS items that participants endorsed at times when depressed mood increased over the course of this study. Similarly, cross-sectional studies in a variety of clinical and non-clinical populations have shown that individuals who are more depressed often report more subjective cognitive difficulties (Chamelian & Feinstein, 2006; Santangelo et al., 2014; Zlatar, Moore, Palmer, Thompson, & Jeste, 2014) and show a greater discrepancy between their subjective and objective cognitive functioning (Serra-Blasco et al., 2019; Thames, Becker, et al., 2011) compared to those with less depressive symptoms. At first glance, this is somewhat in contrast to the non-significant between-person effect of average depressed mood on proportion of reported cognitive difficulties in our mixed effects logistic regression model. That is, participants who were more depressed on

average during the 14-day EMA monitoring period did not report cognitive difficulties more frequently than those who were less depressed on average. However, this highlights the strength in longitudinal designs such that we are able to distinguish within-person effects from between-person effects whereas cross-sectional studies cannot. Our results emphasize that self-reported cognitive difficulties are more strongly related to internal *changes* in depressed mood, rather than a person's average level of depression.

Finally, inconsistent with our last hypothesis, we did not find engagement in cognitively demanding activities to be associated with greater likelihood of reporting cognitive difficulties. In contrast, results showed that doing a cognitively demanding activity was related to *lower* likelihood of reporting concurrent cognitive difficulties (i.e., attention difficulties, specifically), and this effect did not differ by neurocognitive impairment status. The directionality of our original hypothesis was based on the postulation that among those with objective neurocognitive impairment, individuals may only encounter cognitive difficulties when doing an activity that challenges them. In fact, this relationship was shown in a recent pilot study by our group in which we retrospectively assessed engagement in cognitively demanding activities via a self-report measure (Paolillo et al., 2019). Data from that study demonstrated that among neurocognitively impaired participants, greater frequency of cognitively demanding activities was related to worse subjective cognitive decline; however, this relationship was not demonstrated among those who were neurocognitively normal. On the other hand, several studies have reported beneficial effects of engaging in cognitively demanding activities on objective neurocognitive functioning (Allard et al., 2014; Brown et al., 2016; Verghese et al., 2003; Wilson, Segawa, Boyle, & Bennett, 2012). Another recent EMA study from our group even showed a real-time within-person positive association between cognitively demanding

activities and objective neurocognition, such that engagement in cognitively demanding activities was related to better concurrent performance on mobile cognitive tests of executive functioning and verbal learning within persons (L. M. Campbell et al., 2020). Thus, it is possible that our finding reflects participants' accurate perception of their neurocognition when engaging in a cognitively demanding task.

4.3 Use of the Portable Alcohol Breathalyzer

Ratings from the post-study feedback questionnaire suggest that participants found it acceptable to use the breathalyzer for the duration of the study. On average, they reported "somewhat" enjoying the breathalyzer, finding it "somewhat" helpful, and being "somewhat" willing to use the breathalyzer again in the future. Notably, the majority of participants did not think using the breathalyzer was challenging, nor did it interfere with their activities. In terms of feasibility, using the breathalyzer appeared to be almost as feasible as completing EMA surveys, with participants using the breathalyzer a median of 98% of the times that they concurrently completed an EMA survey. Responses from the post-study feedback questionnaire showed that participants were not always able to concurrently use the breathalyzer when completing an EMA survey due to logistic barriers such as forgetting to bring it with them, having difficulty using the breathalyzer, dead batteries in the breathalyzer, and not wanting to use it in public. This slightly lower breathalyzer use rate (compared to that of EMA survey completion) differs from findings reported in a recent study that specifically examined the feasibility of using smartphones and mobile breathalyzers to monitor alcohol use among PWH (Lauckner, Taylor, Patel, & Whitmire, 2019). Lauckner and colleagues found that, on average, participants completed a greater number of breathalyzer readings than mobile surveys over the duration of their study. Of note, in contrast

to our study asking participants to use the breathalyzer during the EMA survey (i.e., the last item on the survey), participants' breathalyzer usage was not tied to the mobile survey in Lauckner and colleagues' study, possibly improving breathalyzer adherence rates. Our result showing slightly lower adherence rates to the breathalyzer, however, is consistent with other studies attempting to use active (i.e., requiring participants' active interaction with an assessment tool), objective measures of behavior in conjunction with subjective reports. For example, several studies from our group (PI: Raeanne C. Moore, PhD) have shown slightly lower rates of adherence to objective mobile cognitive tests compared to that of the concurrently administered EMA surveys (L. M. Campbell et al., 2020). In other studies that have assessed medication adherence among PWH using both real-time self-report (i.e., via text messaging) and an objective measure (i.e., Medication Event System Monitoring TrackCaps [MEMS caps]), MEMS cap use appeared to be somewhat lower than the number of text message responses (D. J. Moore et al., 2018). As wearable technology continues to develop, future studies wishing to obtain objectively measured alcohol use may instead benefit from passive, continuous monitoring in which participants do not have to actively engage with a measurement tool (e.g., wearable alcohol biosensors; (A. S. Campbell, Kim, & Wang, 2018; Wang, Fridberg, Leeman, Cook, & Porges, 2019).

Regarding validity, the portable alcohol breathalyzer appeared to be a valid measure of alcohol use. First, all recorded breathalyzer-estimated BAC values were within the expected range for each drinking occasion given the corresponding report of number of alcohol drinks consumed (i.e., BACs ranging from 0.00 – 0.22 gram%). The breathalyzer-estimated BACs were also highly correlated with the self-reported alcohol use quantity from the same timepoint, and showed a unit-equivalent relationship consistent with estimates from pharmacokinetic research.

That is, our findings showed that BAC increased by about 0.015 gram% per standard drink on average, which is close to estimates from well-known research showing that BAC increases by an average of 0.025 gram% per standard drink (Koob, Arends, & Le Moal, 2014). Furthermore, additional variability in the relationship between BAC and reported alcohol use in the current study was explained by accounting for the reported amount of time since participants' last alcohol drink. Specifically, our results showed that the relationship between breathalyzer-estimated BAC and self-reported alcohol use quantity was weaker when participants reported a greater amount of time since their last drink. This is highly consistent with the pharmacokinetic properties of alcohol in humans, with BACs known to decrease at a constant rate ranging from about 0.010 to 0.035 gram% per hour (after ceasing alcohol use) depending on both biological properties (e.g., age, sex, body fat) and alcohol dosing (A. W. Jones, 2019). Thus, this finding further supports the validity of the current portable breathalyzer as an objective real-time measure of alcohol consumption. Until wearable alcohol biosensing technology improves enough to accurately estimate BAC (Wang et al., 2019), portable alcohol breathalyzers appear to be an acceptable, feasible, and valid way to objectively measure alcohol use.

4.4 Adherence to EMA, Reductions in Alcohol Use, and Study Feedback: Informing Future Studies

Adherence to the EMA protocol was high and comparable to that of other substance using samples (A. Jones et al., 2019; Shiffman, 2009) and other samples with HIV (R. C. Moore et al., 2017; Shacham et al., 2019; Smiley, Milburn, Nyhan, & Taggart, 2020). We also found that adherence was not related to demographic factors, alcohol use data, or neurocognitive impairment status. Notably, however, we observed that participants were increasingly less likely

to complete an EMA survey over time. Specifically, participants were about 10% less likely to complete EMA surveys with each passing study day. Although many EMA studies do not report on how adherence to the EMA protocol may change over time, our finding is consistent with the ones that do, as these have also reported a tendency for EMA adherence to decrease over time (Comulada et al., 2018; Husain et al., 2019; Moitra, Gaudiano, Davis, & Ben-Zeev, 2017; Mulvaney et al., 2013). We believe this is an important metric to include in any EMA study because it can inform optimal study durations for various clinical populations. While our study duration of 14 days was relatively short, it is possible that a slightly shorter duration may have maximized EMA adherence and minimized participant burden while preserving ability to capture within-person variability.

Importantly, data also revealed an incidental finding regarding alcohol use over time. That is, we found a reduction in reported alcohol use within persons over the duration of the 14-day EMA monitoring period. This is an important finding to highlight given the potential clinical relevance for decreasing alcohol use among heavy drinkers with HIV. Although this study was not intended to have any intervening effects on participants' alcohol use patterns, previous research has well documented the effect of self-monitoring on behavioral change. For example, self-monitoring interventions have shown to be effective for weight loss (Burke, Wang, & Sevick, 2011) and increasing physical activity (Compernolle et al., 2019; Kanejima, Kitamura, & Izawa, 2019), with some evidence suggesting that self-monitoring may also be helpful to reduce substance use either alone or as part of a multi-component intervention (Staiger, O'Donnell, Liknaitzky, Bush, & Milward, 2020). The level of alcohol reduction over time in the current study was very small, with a reduction of about 0.03 drinks per day on average throughout the 14-day EMA monitoring period; however, this reduction could yield clinically meaningful levels

over a longer period of self-monitoring (e.g., 6 months). In fact, there is at least one ongoing study examining a 6-month self-monitoring intervention for decreasing substance use (Scott, Dennis, & Gustafson, 2017). Given the high acceptability and feasibility of self-monitoring via smartphone apps or text-message prompts as shown in this current study and others (Bertholet, Daeppen, McNeely, Kushnir, & Cunningham, 2017; Swendeman et al., 2020), this is certainly an area of research worth examining further.

Study feedback indicated that, on average, participants enjoyed their experience overall. It is notable that about half of participants did not experience any challenges during the study, while the rest reported only mild logistic difficulties (e.g., trouble remembering to bring phone/breathalyzer with them, difficulty hearing the survey notification). These challenges are important to evaluate for informing future EMA studies in this population. To maximize EMA survey completion, future studies may consider attempting to troubleshoot these common challenges during the first study visit before the EMA monitoring period. For example, future studies could ensure that the phone's notification volume is loud enough and/or create a plan for participants to carry the device in their pocket or purse. Our participants also reported that the study activities did not interfere with their normal activities, which is important to consider in the context of the frequency of EMA surveys in the current study (i.e., four times daily). The current EMA study procedures were based on methods from successful ongoing EMA studies at the HNRP; however, many other EMA studies, especially among substance using populations, prompt participants to complete surveys less frequently (e.g., daily diary; 1-2 times per day; (Shiffman, 2009). The benefits of more frequent assessment include capturing greater within-person variability within each day, gathering more data points for each participant over a fixed study duration, and reducing lengths of time between EMA surveys, which decreases the

likelihood of retrospective recall errors when assessing experiences that happened between surveys (e.g., number of alcohol drinks consumed since last survey). Potential drawbacks to such a high frequency of assessment are greater participant burden and increased likelihood of missed surveys; however, the high EMA adherence rates and positive post-study feedback from our study provide strong evidence to support the feasibility and advantage of four-times-daily assessments in a heavy alcohol using population.

4.5 Limitations and Future Directions

A thorough examination of this study's limitations is necessary to guide future work. First, this study had a very limited sample size. Although the current sample size allowed ample statistical power to detect within-person associations (given the many data points per person), this sample yielded limited statistical power to detect between-person effects, increasing risk for Type II error. Given that only six of our 23 participants were neurocognitively impaired, we were particularly limited in our ability to detect differences between neurocognitive impairment status groups. Future studies in this area would benefit from improving statistical power either by enrolling a larger overall sample and/or recruiting specifically by neurocognitive impairment status to yield a more equal distribution of participants who are neurocognitively impaired and neurocognitively intact. For example, studies that recruit from clinic samples may have access to data from medical charts, where a neurocognitive diagnosis or data from neurocognitive screeners (e.g., Mini-Mental State Exam, Montreal Cognitive Assessment) may already be on record. As an alternative study design, statistical power may also be improved by examining participants over a longer period of time to understand how reported cognitive difficulties (and their relationship to real-time alcohol, mood, and daily activity factors) change as participants'

objective neurocognition changes. For example, a measurement-burst design (Sliwinski, 2008) involves several distinct periods of EMA monitoring (e.g., several times per day for 1-2 weeks) spaced over a much longer period of time (e.g., years). Such a study design would allow the examination of how daily within-person processes change over a long enough period of time during which neurocognitive decline may be observed. Future studies utilizing measurement-burst designs would be able to examine whether participants with objective neurocognitive decline demonstrate changes in the frequency with which they report cognitive difficulties, and whether that intraindividual change differs from that of participants with no observed neurocognitive decline.

Another potential limitation to this study was our use of the EACS screening questions as our primary self-report assessment of cognitive difficulties. For example, there are many other self-report assessments of cognitive difficulties that have been utilized in other studies with PWH and heavy drinkers, such as the Patient Assessment of Own Functioning Inventory (Chelune et al., 1986) or the Everyday Cognition self-report questionnaire (Farias et al., 2008). However, the EACS questions were selected for this study for three important reasons. First, the EACS questions were uniquely developed with the intention of assessing specific deficits that are characteristic among PWH. Second, this assessment is brief with only three questions, making it easy to implement and likely to maximize participant responsiveness in the EMA format. Finally, the EACS questions are the current internationally recommended method of screening for HIV-associated neurocognitive impairment in clinical settings, making their use clinically relevant. Although these items have several advantages, their brevity and limited response options are also drawbacks. With regard to brevity, the use of only three items works well for feasibility in our repeated assessments; however, we may also be missing information

about other cognitive difficulties that are not included in the three items about memory, slowed thinking, and attention (e.g., getting lost, difficulties with language expression and comprehension, difficulties multitasking). Additionally, having only three response options for each item is perhaps the biggest weakness of the EACS questions, as this likely limited our ability to capture more within-person variability in responses. As noted in the Methods, our modified EMA-administered EACS questions yielded a very low proportion of "Yes, definitely" responses (3%). Although there was adequate within-person variability between the other two responses (i.e., "No" and "Somewhat"), the use of additional gradations in the response choices may have improved our ability to examine more fine-grained variations in cognitive difficulties as they relate to both objective neurocognition and real-time predictors. In fact, a recent psychometric study demonstrated that a fewer number of response options (i.e., less than five options) attenuated psychometric precision for a measure of personality among undergraduate students (Simms, Zelazny, Williams, & Bernstein, 2019). Future EMA studies would benefit from using a wider range of response options (i.e., at least six) for all items assessing subjective experiences in order to increase the likelihood of capturing within-person variability.

Related to capturing within-person variability, the timing of our EMA surveys may have been too limited to frequently catch participants during moments of active drinking. For example, there were a number of surveys on which participants reported drinking "4 or more hours ago," meaning that they were actively drinking in the time period *between* surveys, or perhaps were reporting alcohol use that occurred after the last EMA survey from the night before. An alternative method that could have been employed is the use of an event-based sampling strategy, which asks participants to complete an EMA survey every time a specific event occurs (e.g., alcohol consumption; (Shiffman, 2007). While this sampling method has

advantages in being able to capture moments of particular interest to the researcher, there are also methodological difficulties with this. One difficulty with event-based sampling is having to rely on participants to independently complete EMA surveys without a phone-based prompt, which can be difficult for participants to remember to do and often results in missing data (Ziesemer et al., 2020). Another issue with event-based sampling is that it can be difficult to properly define the specific event during which you want a participant to complete an EMA survey (e.g., after the first sip of the first drink vs. after finishing each drink vs. after "feeling inebriated"; (Shiffman, 2007). A potential future direction would be to incorporate both time-based surveys (as were employed in the current study) and event-based surveys. Furthermore, as wearable technology improves, such event-based surveys could even be prompted by a wearable alcohol biosensor (Wang et al., 2019), which would be able to passively and continuously monitor alcohol use and alert a participant to complete an EMA survey after their estimated BAC reaches a certain level.

We were also limited in our ability to make direct conclusions about whether an individual's report of cognitive difficulties was due to acute fluctuations in their objective neurocognition. Although we were primarily interested in how real-time self-reported cognitive difficulties related to neurocognitive impairment status, it is well known that neurocognition can fluctuate throughout the day regardless of clinical neurocognitive impairment status. For example, research has shown that neurocognitive functioning fluctuates not only by time of day (i.e., due to circadian rhythms), but also by stress, sleep, mood, caffeine intake, exercise, alcohol/substance use, and certain daily activities (Brose, Lovden, & Schmiedek, 2014; Brose et al., 2012; Brown et al., 2016; Gamaldo, Allaire, & Whitfield, 2010; Ruxton, 2008; Sliwinski, Smyth, Hofer, & Stawski, 2006; Stenling et al., 2020; Weizenbaum, Torous, & Fulford, 2020).

While these fluctuations are often subtle, with changes that may not reach a level of clinical significance (e.g., performing only milliseconds slower on a task; (L. M. Campbell et al., 2020), it is possible that such fluctuations may be accurately perceived by an individual and lead to their self-report of cognitive difficulties. Future studies examining real-time predictors of cognitive difficulties would benefit from including a real-time measure of objective neurocognition (e.g., mobile cognitive tests; (Germine, Reinecke, & Chaytor, 2019; R. C. Moore, Campbell, et al., 2020; R. C. Moore, Paolillo, et al., 2020; Schweitzer et al., 2017). This would contribute to a better understanding of whether a participant perceives a true change in their objective cognition as a result of a particular factor (e.g., alcohol use), or whether their self-reported cognitive difficulty is discrepant from their objective performance on a mobile cognitive test.

This study was also limited in that we did not include any comparison groups to examine whether the studied relationships among objective neurocognition, cognitive difficulties, alcohol use, mood, and daily activities differ by HIV status or by alcohol drinking status (e.g., non-drinkers vs. light drinkers vs. heavy drinkers). Although this study was designed specifically to examine PWH who drink heavily, as they are at increased risk for neurocognitive and everyday functioning impairments, our focus on this specific group limits generalizability to other populations. Furthermore, our generalizability within the population of PWH who drink heavily is somewhat limited because of two other factors: 1) possible selection bias, and 2) exclusion of individuals with co-occurring other substance use disorders. First, our enrollment rate for this study was low, and only 23 participants were retained for the duration of the study out of the almost 200 individuals who we attempted to contact. This suggests that the 23 participants in our study may represent the result of a selection bias in which these participants may be more stable (e.g., medically, cognitively, financially, housing) than the many participants who were not

enrolled. Thus, it is possible that our findings may not generalize to the wider population of PWH who drink heavily who may be likely to have lifestyle instabilities (e.g., inconsistent contact information, homelessness). Next, research has shown that individuals with heavy alcohol use are likely to also use other substances heavily (Falk, Yi, & Hiller-Sturmhöfel, 2008; Jordan et al., 2018). Thus, future studies would be needed to determine the reliability of our findings in polysubstance using populations.

4.6 Summary and Clinical Implications

This EMA study showed that, among PWH who drink heavily, real-time self-reported cognitive difficulties were related to individuals' overall objectively-measured neurocognitive functioning. Despite being highly sensitive, however, real-time self-reported cognitive difficulties did not show a statistically significant improvement in identifying neurocognitive impairment compared to that of self-reported cognitive difficulties assessed retrospectively during an in-person visit. These results suggest that cognitive difficulties reported via EMA may better detect subtle cognitive deficits that do not reach a clinically impaired threshold, which has important clinical implications for early detection of neurocognitive decline. Importantly, this study also uniquely showed that real-time self-reported cognitive difficulties are highly influenced by concurrent daily experiences, including alcohol use, depressed mood, and engagement in cognitively demanding activities, regardless of neurocognitive impairment status. Taken together, these results suggest that self-reported cognitive difficulties assessed via EMA may have some clinical utility to identify individuals in need of neuropsychological assessment, early intervention, and a potentially higher level of care. Although certain daily experiences related to increased likelihood of reporting cognitive difficulties may contribute to a higher false

positive rate, real-time self-reported cognitive difficulties appeared to have high sensitivity for identifying risk of neurocognitive impairment. Given the high feasibility of EMA to assess experiences related to one's neurocognitive and everyday functioning, especially in populations that are otherwise difficult to follow in a clinic setting (e.g., heavy alcohol / substance users; (Lipari, Park-Lee, & Van Horn, 2016; Saloner & Karthikeyan, 2015), further work is needed to determine whether these results are replicated and strengthened in larger samples better powered to detect statistically significant associations. In addition, our exploratory examination of a portable alcohol breathalyzer showed that using such a device to objectively measure alcohol use is acceptable, feasible, and valid. Considering this alongside our incidental finding that alcohol use declined over time with our self-monitoring protocol, portable breathalyzers may be a highly useful tool in future alcohol intervention studies. In summary, findings from this study suggest better ways to monitor neurocognitive and everyday functioning in high-risk populations, which, if replicated in future research, may have downstream positive effects on both individual and public health.

APPENDIX 1: Full EMA Survey

Note: Text shown in red font does not appear on the actual EMA survey.

1. Since the last survey, have you experienced memory difficulties?

   No
   Somewhat
   Yes, definitely

2. Since the last survey, have you felt slow when reasoning, planning activities, or solving problems?

   No
   Somewhat
   Yes, definitely

3. Since the last survey, have you had any difficulties paying attention?

   No
   Somewhat
   Yes, definitely

4. Since the last survey, how many alcoholic beverages did you drink?

   0
   1
   2
   3
   4
   5
   6
   7
   8
   9
   10
   11
   12
   13
   14
   15+

5. How many hours ago did you last drink alcohol?

Less than 0.5 hours ago
0.5 hours ago
1 hour ago
1.5 hours ago
2 hours ago
2.5 hours ago
3 hours ago
3.5 hours ago
4 or more hours ago

6. Where are you right now?

At my home
At home of family
At home of friends
At work
At outpatient medical visit
In hospital
At community center
In public business/store
In vehicle
Outside walking
In class/educational setting
Inside other
Outside other

If responded "At home" on Q6:

7. What are you doing? Select all that apply

Preparing food
Eating or drinking
Cleaning my home/room
Laundry
Budgeting or paying bills
Showering or grooming
Changing Clothes
Watching TV
Resting
Social media (e.g., facebook, twitter)
Shopping online
Other internet/computer/tablet use
Reading, writing, or journaling
Exercising
Gardening
Other physical leisure
Other non-physical leisure

If responded with anything but "At home" on Q6:

What are you doing? Select all that apply

Eating or drinking out
Working (paid)
Volunteering
Unpaid work
Schoolwork
Looking for a job
Shopping
Entertainment (cinema, sports, etc.)
Riding in a bus, trolley, car or van
Social Interactions
Visiting the beach or park
Visiting family or friends
Exercising
Other physical leisure
Watching TV
Resting
Social media (e.g., facebook, twitter)

Social Interactions
Working (paid)
Volunteering
Unpaid work
Schoolwork
Meditating
Private religious activities
Listening Music
Smoking
Arts and crafts
Playing a musical instrument
Looking for a job
Nothing
Other

Other internet/computer/tablet use
Reading, writing, or journaling
Other non-physical leisure
Meditating
Private religious activities
Meeting (church, AA, etc.)
Listening Music
Smoking
Doing laundry at Laundromat
Nothing
Other

8. Since the last survey, have you done any of the following?
(Select all that apply)

Paying bills/Managing finances
Solving a new problem (e.g., broken appliance, schedule conflict)
Attempting a new task
Multi-tasking (i.e., doing 2 or more tasks at once)
Prioritizing and completing tasks in order of importance
Planning (e.g., planning an activity, transportation)
Complex cooking (e.g., new recipe, multi-dish meals)
Shopping without a list
Navigating to a new place
Participating in social interactions
Reading
Writing
Playing games or doing puzzles
Other cognitively-demanding activity: *[Fillable text box]*
None

8a. If anything other than "None" was selected for Q8:
Which activity was the most cognitively demanding?

[All previously selected answers are given as response options]

8b. If anything other than "None" was selected for Q8:
How cognitively demanding was this activity for you?

[visual analog scale] 1 (Not at all) to 10 (Extremely)

9. What is your pain level right now?

[visual analog scale] 1 (Minimal or no pain) to 10 (Severe pain)

10. I feel tired…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

11. I feel happy…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

12. I feel depressed…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

13. I feel worthless…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

14. I feel cheerful…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

15. I feel anxious…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

16. I feel worried…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

17. I feel relaxed…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

18. I feel stressed…
    Not at all
    A little bit
    Somewhat
    Quite a bit
    Very much

19. Since the last survey, have you taken or used any of the following substances? (select all that apply)
    Caffeine
    Tobacco
    Cannabis/marijuana
    Cocaine/crack
    Crystal/meth
    Ecstasy/Molly
    Heroin
    Other street drug(s)
    Prescription drugs not prescribed to me
    No substance/drug use

20. Only asked on the first survey of the day:
    Do you intend to take your medication today?

    Yes
    No

21. Only asked on the last survey of the day:
    Did you take your medication today?

    Yes, I took it on-time (within 2 hours of intended time)
    Yes, I took it early or late (>2 hours before or after intended time)
    No

22. Please use your alcohol breathalyzer now. Enter your estimated blood alcohol content (BAC) that appears on the display of the breathalyzer.

Unable to use breathalyzer right now
0.00
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.10
0.11
0.12
0.13
0.14
0.15
0.16
0.17
0.18
0.19
0.20
0.21
0.22
0.23
0.24
0.25
0.26
0.27
0.28
0.29
0.30 or higher

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