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

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

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

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

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

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

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INTRODUCTION

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

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

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

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

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

METHODS

Participants and Design

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

Demographic Evaluation

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

Substance Use and Psychiatric Evaluation

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

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

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

Neuromedical Evaluation

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

Neuropsychological Evaluation

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

Statistical Analyses

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

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

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

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

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

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

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

RESULTS

Study Cohort

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

Cannabis Characteristics

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

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

NCI Across HIV and Cannabis Groups

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

Cannabis, HIV, and Age on NCI

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

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

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

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

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

Cannabis on Cognitive Domains by HIV Status

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

DISCUSSION

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

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

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

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

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

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

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

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

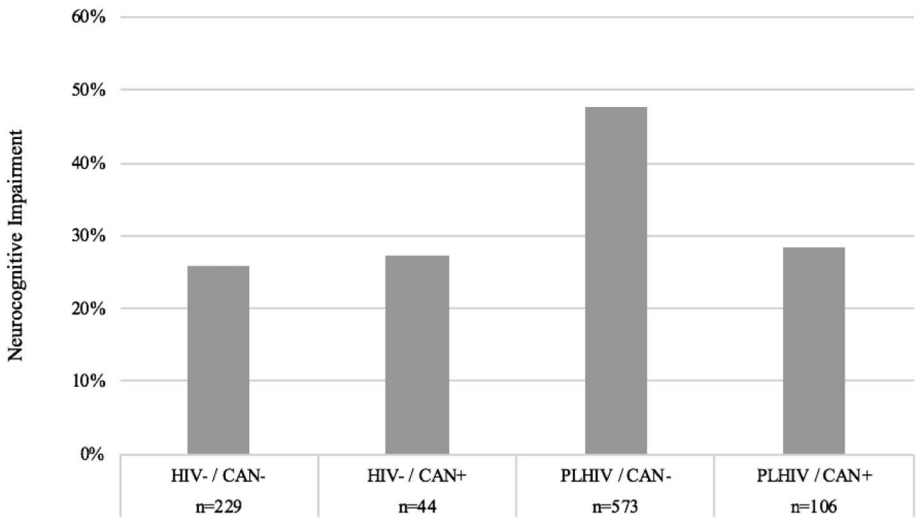

FIGURE 1. Rates of NCI stratified by HIV status (HIV−/PLHIV) and cannabis exposure (CAN−/CAN+). HIV–, People Living without HIV; PLHIV, People Living with HIV; CAN+, cannabis exposure group; CAN–, non-cannabis exposure group.

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

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

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

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

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

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

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

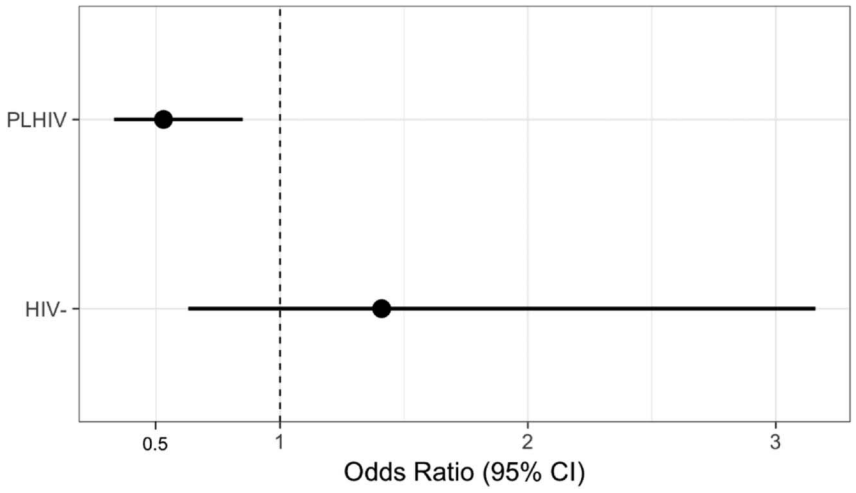

FIGURE 2. Odds ratios for effect of cannabis exposure on NCI in people living with HIV (n = 679) and HIV– individuals (HIV−) (n = 273). Cannabis exposure was associated with lower odds of NCI among PLHIV (OR = 0.53, 95% CI = 0.33 to 0.85, $P = 0.009$) and was not related to NCI among HIV− (OR = 1.41,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

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

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

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