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Binge drinking relates to worse neurocognitive functioning among adults aging with HIV

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ABSTRACT

Objective: Given the aging population of people with HIV (PWH), along with increasing rates of binge drinking among both PWH and the general older adult population, this study examined the independent and interactive effects of HIV, binge drinking, and age on neurocognition.

Method: Participants were 146 drinkers stratified by HIV and binge drinking status (i.e., ≥ 4 drinks for women and ≥5 drinks for men within approximately 2 hours): HIV+/Binge+ (n = 30), HIV-/Binge+ (n = 23), HIV+/Binge- (n = 55), HIV-/Binge- (n = 38). All participants completed a comprehensive neuropsychological battery measuring demographically-corrected global and domain-specific neurocognitive T-scores. ANCOVA models examined independent and interactive effects of HIV and binge drinking on neurocognitive outcomes, adjusting for overall alcohol consumption, lifetime substance use, sex, and age. Subsequent multiple linear regressions examined whether HIV/Binge group moderated the relationship between age and neurocognition.

Results: HIV+/Binge+ participants had worse global neurocognition, processing speed, delayed recall, and working memory than HIV-/Binge- participants (ps<0.05). While there were significant main effects of HIV and binge drinking, their interaction did not predict any of those neurocognitive outcomes (ps>0.05). Significant interactions between age and HIV/Binge group showed that HIV+/Binge+ participants demonstrated steeper negative relationships between age and neurocognitive outcomes of learning, delayed recall, and motor skills compared to HIV-/Binge- participants (ps<0.05).

Conclusions: Results showed adverse additive effects of HIV and binge drinking on neurocognitive functioning, with older adults demonstrating the most vulnerability to these effects. Findings support the need for interventions to reduce binge drinking, especially among older PWH.

Keywords (6 mesh terms): HIV; AIDS; alcohol-related disorders; aged; cognitive dysfunction; neurocognitive disorders

INTRODUCTION

People with HIV (PWH) are twice as likely to engage in heavy alcohol use and two to three times more likely to meet criteria for an alcohol use disorder (AUD) in their lifetime than the general population (Galvan et al., 2002; Justice, 2010). Heavy alcohol use not only promotes the transmission of HIV through sexual risk-taking behavior and nonadherence to antiretroviral therapy (ART; (Cook & Clark, 2005; Paolillo, Gongvatana, Umlauf, Letendre, & Moore, 2017; Wen, Balluz, & Town, 2012), but also directly exacerbates HIV disease burden by compromising the efficacy of ART and increasing systemic inflammation (Bryant, 2006; Miguez, Shor-Posner, Morales, Rodriguez, & Burbano, 2003; Shuper et al., 2010; So-Armah et al., 2019). In addition to increased risk for physical illness (e.g., liver disease and cardiovascular risk; (Molina, Simon, Amedee, Welsh, & Ferguson, 2018; Price & Thio, 2010), there is substantial evidence indicating that comorbid HIV and heavy alcohol use is more detrimental to brain structure and results in higher rates of neurocognitive impairment than either condition alone (Rosenbloom, Sullivan, & Pfefferbaum, 2010; Rothlind et al., 2005; Sullivan & Pfefferbaum, 2019).

The impact of comorbid HIV and heavy alcohol use on the central nervous system (CNS) is especially important to consider in the context of aging. The population of older adults with HIV is rapidly growing; approximately 48% of PWH in the U.S. are aged 50 and older and the prevalence of PWH over the age of 65 increased by 56% from 2012 to 2016 (Centers for Disease Control and Prevention, 2018). Trajectories of neurocognitive and brain aging appear to be steeper in PWH (Cohen, Seider, & Navia, 2015), possibly due to chronic inflammation and immune dysfunction, long-term use of ART, frailty, and cardiometabolic comorbidities (Pathai, Bajillan, Landay, & High, 2014). In addition to HIV, rates of alcohol use and misuse are also

rising in older adults (Breslow, Castle, Chen, & Graubard, 2017; Han, Moore, Sherman, Keyes, & Palamar, 2017). The neurocognitive and physical consequences of heavy alcohol use are more severe among older than younger adults, and several studies also report accelerated neurocognitive and brain aging in adults with AUD (Pfefferbaum et al., 2018; Sullivan & Pfefferbaum, 2019). While mechanisms underlying these effects are poorly understood, older adults may be more vulnerable to alcohol-related neurotoxicity due to a reduced capacity to metabolize alcohol, lower total-fluid volume, and diminished physiologic reserve to withstand biological stressors (Meier & Seitz, 2008; Strandberg, Trygg, Pitkälä, & Strandberg, 2018).

Altogether, these studies support a hypothesis that PWH may be particularly susceptible to the combined deleterious effects of aging and heavy alcohol use. For example, in a recent longitudinal report, Pfefferbaum et al. (2018) reported that PWH (aged 25-75 years) with comorbid alcohol dependence exhibited faster declines in brain volumes in the midposterior cingulate and pallidum above and beyond either condition alone. There is considerable heterogeneity, however, in profiles of neurocognitive functioning across individuals with HIV and AUD (Devlin & Giovannetti, 2017; Sullivan & Pfefferbaum, 2019). Patterns of alcohol consumption rarely remain static throughout the course of an AUD, but rather are often characterized by discrete periods of heavy use. This episodic pattern of heavy consumption may similarly impact the stability of HIV disease (Cook et al., 2017), which may in part explain why some PWH with AUD exhibit substantial neurocognitive deficits while others remain neurocognitively intact. Self-report estimates of alcohol use, however, often fail to predict neurocognitive performance (Durvasula, Miller, Myers, & Wyatt, 2001; Fama, Rosenbloom, Nichols, Pfefferbaum, & Sullivan, 2009; Rothlind et al., 2005). Methods for quantifying heavy drinking are also inconsistent across studies. For example, some studies classify individuals

based on DSM criteria for AUD whereas others define heavy drinking based on "high-risk" patterns of weekly consumption (e.g., >7 drinks/week for women, >14 drinks/week for men). These methods characterize the chronicity of drinking and psychosocial aspects of alcohol misuse, but they are suboptimal for quantifying discrete periods of heavy exposure and high-level intoxication that may confer higher risk for neurocognitive dysfunction. Binge drinking, defined by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as 4 or more drinks for women and 5 or more drinks for men within approximately 2 hours, may more precisely capture discrete episodes of heavy exposure. The relationship between binge drinking and neurocognitive functioning remains poorly understood across the lifespan and particularly in the context of HIV.

Thus, the current study examined two primary aims to better understand the impacts of HIV, binge drinking, and age on neurocognitive functioning. The first study aim examined the independent and interactive effects of HIV and binge drinking on global and domain-specific neurocognitive functioning. We hypothesized that: 1) neurocognitive performance would be poorer with each additional risk factor such that the HIV-/Binge- group would exhibit the best neurocognition, followed by the single-risk groups (HIV+/Binge- and HIV-/Binge+), and finally the dual-risk (HIV+/Binge+) group; and 2) these group differences would be explained by a detrimental synergistic (i.e., not just additive) effect of HIV and binge drinking on neurocognition. The second study aim examined whether the strength of the association between age and neurocognition differed by HIV/Binge group. We hypothesized that: 1) older age would relate to poorer neurocognition; and 2) that this negative relationship would be strongest in the HIV+/Binge+ group.

METHODS

Participants

Participants included 85 PWH and 61 HIV- adults who reported drinking alcohol (i.e., at least 1 drink) in the 30 day period prior to their study visit. Participants were further stratified based on their recent binge drinking status, resulting in the following four groups: HIV+/Binge+ (n = 30), HIV-/Binge+ (n = 23), HIV+/Binge- (n = 55), HIV-/Binge- (n = 38). All participants were enrolled in NIH-funded research studies at the University of California, San Diego's (UCSD) HIV Neurobehavioral Research Program, and gave written informed consent as approved by the UCSD Institutional Review Board. The current cross-sectional study is a secondary analysis of data from each participant's baseline visit at the HIV Neurobehavioral Research Program from 2003-2019. Exclusion criteria for the current analysis were: 1) current diagnosis of non-alcohol substance use disorders (SUDs; i.e., cannabis, cocaine, hallucinogen, inhalant, opioid, sedative, and methamphetamine); 2) diagnosis of psychotic or mood disorder with psychotic features; 3) presence of a neurological or medical condition that may negatively affect cognitive functioning, such as traumatic brain injury, stroke, or epilepsy; 4) positive urine toxicology for illicit drugs (excluding cannabis) or positive Breathalyzer test for alcohol on the day of study visit; 5) report of no "recent" alcohol consumption (in the last 30 days).

Measures

Alcohol Use, Substance Use, and Psychiatric Assessment

A modified timeline follow-back interview was used to assess drinking behavior in the last 30 days (e.g., total number of drinking days, total number of drinks). Binge drinking was assessed per NIAAA criteria for binge drinking (i.e., ≥ 4 drinks for women and ≥5 drinks for men within approximately 2 hours). Binge drinking behavior was dichotomized such that

participants who had any binge drinking episode in the last 30 days were classified as binge drinkers (Binge+). Lifetime history of alcohol exposure, including quantity and frequency, was assessed via a semi-structured timeline follow-back interview that evaluates drinking patterns across different periods in an individual's life.

Current depressive symptoms were assessed using the Beck Depression Inventory-II, a self-report measure (Beck, Steer, & Brown, 1996). The Composite International Diagnostic Interview (CIDI, v2.1) was administered to evaluate current and lifetime (occurring >12 months prior) mood and SUDs (World Health Organization, 1998). Notably, the parent grants from which baseline data were drawn were funded prior to the publication of the DSM 5. Therefore, diagnoses were made in accordance with DSM-IV criteria where alcohol/substance abuse is met when participants report recurring problems (e.g., interpersonal, work-related, legal) as a result of continued alcohol/substance use; and alcohol/substance dependence is met when participants experience symptoms of tolerance, withdrawal, and/or compromised control over their alcohol/substance use (American Psychiatric Association, 2000). In order to remain consistent with the current DSM 5 criteria and nomenclature, alcohol/substance abuse and dependence criteria were combined to capture AUD and SUD.

Neuromedical Assessment

Participants were tested for HIV by enzyme-linked immunosorbent assay (ELISA) with Western Blot confirmation. All participants completed a comprehensive medical evaluation including self-report measures, structured neurological and medical evaluations, and blood samples to assess the presence of medical comorbidities (i.e., hepatitis C) and HIV disease characteristics. HIV viral load in plasma was measured using reverse transcriptase-polymerase

chain reaction (RT-PCR; Amplicor, Roche Diagnostics, Indianapolis, IN), where viral load was deemed undetectable below 50 copies/mL.

Neurocognitive Assessment

Participants were administered a comprehensive battery of neurocognitive assessments measuring global and domain-specific neurocognitive performance: global function, verbal fluency, executive function, processing speed, learning, delayed recall, working memory, and motor skills (Heaton et al., 2010). Raw scores from each neuropsychological test were converted into demographically-corrected (i.e., age, education, sex, and race/ethnicity) T-scores (M = 50, SD = 10). Global and domain-specific continuous T-scores were derived from averaging the demographically-corrected T-scores across all tests and within each neurocognitive domain, respectively (Antinori et al., 2007; Heaton, Miller, Taylor, & Grant, 2004; Heaton, Taylor, & Manly, 2003). These global and domain-specific T-scores were used as primary outcomes for comparisons of neurocognition between HIV/Binge groups.

Statistical Analyses

Demographic, psychiatric, medical, alcohol and substance use, and HIV disease characteristics were compared between the four HIV/Binge groups using analysis of variance (ANOVA) or chi-square tests, as appropriate. Pair-wise comparisons were conducted to follow up on significant omnibus results using Tukey's Honest Significant Difference (HSD) tests for continuous outcomes or Bonferroni adjustments ($\alpha = 0.05/4 = 0.0125$) for categorical outcomes. Nonparametric Wilcoxon tests were used to for continuous variables with skewed distributions.

To examine the first study aim, one-way ANOVA and Tukey's HSD tests were used to compare mean global and domain neurocognitive T-scores between the four HIV/binge drinking groups. For any significant one-way ANOVA result, a 2 x 2 factorial ANCOVA was used to

model independent and interactive effects of HIV and binge drinking status, covarying for total drinks consumed in the last 30 days (to better separate the independent effects of binge drinking from total alcohol consumption) and any demographic or non-alcohol-related clinical characteristics that differed between groups at $p<0.05$ (i.e., age, sex, and lifetime history of non-alcohol SUDs). These demographic covariates were included to increase confidence that any observed difference in neurocognition between HIV/Binge groups would not be attributable to confounding effects of age and sex that may that may exist above and beyond the T-scores' demographic corrections. To further support any findings indicating additive main effects, Jonckheere-Terpstra tests for ordered alternatives examined whether there was a statistically significant negative relationship between the number of risk factors (i.e., 0 risks = HIV-/Binge-; 1 risk = HIV-/Binge+ or HIV+/Binge-; 2 risks = HIV+/Binge+) and neurocognitive performance (e.g., Iudicello et al., 2012). Finally, to examine the second study aim, multiple linear regressions modeled the interaction between age and HIV/Binge status group on global and domain-specific T-scores, also covarying for total drinks consumed in the last 30 days, sex, and lifetime history of non-alcohol. Our examination of age as a predictor of demographically-corrected T-scores will allow understanding of how the effect of age in certain vulnerable groups (e.g., PWH who binge drink) may go above and beyond that of normal controls on whom demographic corrections were based. Parametric statistics were used because the outcome variables (i.e., global and domain-specific neurocognitive T-scores) were continuous and had normal distributions in each HIV/Binge group. All analyses were performed using R, version 3.5.0.

RESULTS

Demographic and clinical factors by HIV/Binge group are displayed in Table 1. The HIV-/Binge- group was younger than both HIV+ groups ($p<0.001$), and the HIV+/Binge+ group

had a higher proportion of men compared to the two HIV- groups (p=0.017). Regarding alcohol and substance use characteristics, the two Binge+ groups had significantly higher quantity and frequency of alcohol use in the last 30 days, higher proportions of current and lifetime AUD, higher lifetime quantity and frequency of alcohol use, and a higher proportion of lifetime non-alcohol SUDs compared to those of both Binge- groups (ps<0.001). Alcohol use characteristics, including frequency of alcohol binges in the last 30 days, did not differ between the HIV-/Binge+ and HIV+/Binge+ groups (p>0.05). All psychiatric, medical, and HIV disease characteristics were comparable across groups.

ANOVA results revealed a significant omnibus difference across HIV/Binge groups in mean global neurocognitive function ($F(3,142) = 4.39$, $p = 0.006$), which was driven by domain-specific differences in processing speed ($F(3,142) = 3.86$, $p = 0.011$), delayed recall ($F(3,142) = 3.27$, $p = 0.023$), and working memory ($F(3,142) = 3.851$, $p = 0.011$). For each of those neurocognitive outcomes with a significant omnibus result, follow-up pairwise comparisons showed significant differences between only the HIV-/Binge- and the HIV+/Binge+ groups, with HIV+/Binge+ participants exhibiting poorer performance (Figure 1). Results of the 2 x 2 factorial ANCOVAs are shown in Table 2. Additive main effects of HIV status and binge drinking status were detected on global function and processing speed, however none of the interactions between HIV and binge drinking status on neurocognitive outcomes reached statistical significance. Additive main effects of HIV and binge drinking were further supported by results from Jonckheere-Terpstra tests indicating significantly lower global ($JT = 2303.5$; $p < 0.001$) and processing speed ($JT = 2414.0$; $p = 0.001$) performance by each increase in risk factor count (i.e., 0 risks = HIV-/Binge-; 1 risk = HIV-/Binge+ or HIV+/Binge-; 2 risks = HIV+/Binge+). Binge drinking was also a significant predictor of delayed recall and working

memory. Of note, the effects of binge drinking on neurocognition were not attenuated by accounting for total drinks in the last 30 days, which did not significantly relate to any neurocognitive outcome (*p*s>0.05; Table 2).

Multiple linear regression revealed significant interactions between age and HIV/Binge group on neurocognitive outcomes of learning (b=-0.37, *p*=0.044), delayed recall (b=-0.42, *p*=0.021), and motor skills (b=-0.66, *p*=0.003) (Table 3). Specifically, the association between age and each of those three neurocognitive outcomes was significantly more negative in the HIV+/Binge+ group (Learning: b=-0.43, *p*=0.001; Recall: b=-0.47, *p*<0.001; Motor: b=-0.63; *p*<0.001) compared to that of the HIV-/Binge- group (Learning: b=-0.06; *p*=0.647; Recall: b=-0.05, *p*=0.690; Motor: b=0.04; *p*=0.811) (Figure 2). This interaction was not significant for any other neurocognitive outcome (i.e., global cognition, verbal fluency, executive function, processing speed, and working memory). Additional analyses comparing age-slopes between all groups revealed that the difference in age-slopes between the HIV+/Binge- and HIV-/Binge- groups approached significance for delayed recall (*p*=0.072) and motor skills (*p*=0.082), such that the HIV+/Binge- group had a stronger relationship between age and those neurocognitive domains. Total drinks in the last 30 days, sex, and lifetime non-alcohol SUD were not significant predictors of any neurocognitive outcomes. In addition, all results held when also covarying for current and lifetime AUD. Notably, when the age range of the entire sample is restricted to a maximum of 60 years old (i.e., so that all groups have the same upper age limit and comparable mean ages; HIV-/Binge-: M_{age} = 35.5, SD = 11.9; HIV+/Binge-: M_{age} = 41.2, SD = 8.2; HIV-/Binge+: M_{age} = 40.4, SD = 11.8; HIV+/Binge+: M_{age} = 41.6, SD = 10.9; F[3,124] = 2.6, *p* = 0.06), the interaction between age and HIV/Binge group (i.e., HIV+/Binge+ vs. HIV-/Binge-)

remains significant for neurocognitive outcomes of delayed recall (*b*=-0.46, *p*=0.02) and motor skills (b=-0.64, *p*=0.01) while it becomes marginally significant for learning (b=-0.32, *p*=0.09).

CONCLUSIONS

Given the rapidly growing population of older adults with and without HIV along with the increased rates of binge drinking among them, studying the combined effects of HIV and binge drinking across the lifespan is timely and important. Partially consistent with our first hypothesis, the HIV+/Binge+ group demonstrated the worst global neurocognitive functioning (driven by domain-specific findings in processing speed, delayed recall, and working memory); however, the combined effects of HIV and binge drinking on global neurocognitive functioning exhibited an additive, rather than synergistic, pattern (as indicated by significant main effects of both HIV status and binge drinking status without a significant interaction effect). Consistent with our second hypothesis, we found a novel interaction with age and HIV/Binge drinking group such that the HIV+/Binge+ group displayed a stronger negative relationship between age and three domain-specific neurocognitive outcomes (i.e., learning, delayed recall, and motor skills) compared to the HIV-/Binge- group. Importantly, the alcohol-related detriments to neurocognition appeared to be specific to binge drinking, as total 30-day alcohol consumption was not a significant independent predictor of any neurocognitive outcome in our statistical models. These findings suggest that recent, discrete episodes of heavy alcohol exposure relate to poorer brain function and highlight the need for interventions to reduce binge drinking behavior among PWH, especially older PWH, in order to promote cognitive health.

The findings showing additive main effects of HIV and binge drinking are consistent with several other studies demonstrating additive, but not synergistic, effects of HIV and heavy alcohol use on neurocognitive functioning (Rosenbloom et al., 2010). In fact, there is only one

study to our knowledge that has shown an interactive effect of HIV and heavy alcohol on neurocognition, specifically in the domains of motor and visuomotor speed (Rothlind et al., 2005). Our finding of HIV/Binge group differences in neurocognitive domains of processing speed, delayed recall, and working memory is also consistent with the frontostriatal and frontolimbic neural damage that has been observed in studies of adults with HIV and heavy alcohol use (Pfefferbaum et al., 2012; Rosenbloom et al., 2010; Sullivan & Pfefferbaum, 2019). As briefly discussed, there are a number of possible mechanisms underlying the relationship between heavy alcohol use and adverse neurocognitive outcomes in HIV, including those related to antiretroviral therapy (e.g., non-adherence; Paolillo et al., 2017); possible pharmacokinetic interactions with alcohol (Simon et al., 2018). Recent research, however, has revealed neuroinflammatory and neuro-immunological effects as major pathways underlying the relationship between heavy alcohol use and neurobiological damage (Crews et al., 2015), with several of these neuroimmune pathways overlapping with effects from HIV (Monnig, 2017). Although these immunobiological underpinnings are still poorly understood in the context of comorbid HIV and heavy drinking, this represents an important line of research needed to develop potential targeted interventions for reducing the incidence and/or severity of neurocognitive impairment in this population.

The current study also uniquely found that the negative relationship between age and neurocognitive functioning was steepest among the PWH who reported binge drinking in the last 30 days, particularly in the domains of learning, delayed recall, and motor skills. Our findings are consistent with what is known about the greater vulnerability to brain atrophy and neurocognitive deficits in older PWH (Clifford et al., 2017; Greene et al., 2015; Valcour et al., 2004) and older adults who drink heavily (Sullivan & Pfefferbaum, 2019; Woods et al., 2016;

Zahr, 2018). Furthermore, this result showing an age by HIV/Binge group interaction is also similar to findings from a previous study in which age was found to be a significant predictor of demographically-corrected episodic memory scores only among individuals with comorbid HIV and AUD (Fama, Sullivan, Sassoon, Pfefferbaum, & Zahr, 2016). Speculation about accelerated aging or neurocognitive decline cannot be made from our data, as they are cross-sectional; however, this result does suggest that older adults are the most susceptible to adverse neuropsychological outcomes in the context of HIV and binge drinking. Notably, this result also held when restricting the maximum age range to 60 years old for all groups, indicating that HIV/ Binge group differences in delayed recall and motor skills emerge even in the earlier stages of older adulthood.

Notably, findings from this report appear to be driven specifically by our binge drinking variable, as total 30-day alcohol consumption did not significantly predict any neurocognitive outcome above and beyond binge drinking. Although there are a dearth of studies examining the specific impact of binge drinking on neuropsychological outcomes compared to that of chronic drinking over a longer span of time, some evidence suggests that the repeated periods of high level of intoxication and withdrawal from binge drinking exacerbates the detrimental neurobiological effects of alcohol (e.g., oxidative stress, proinflammatory and neuroimmune response, and excitotoxicity leading to neuronal damage in frontal and hippocampal regions) (Campanella et al., 2013; Crews et al., 2015; Maurage et al., 2012; Meyerhoff et al., 2004; Petit, Maurage, Kornreich, Verbanck, & Campanella, 2014; Waszkiewicz et al., 2018). Future research is needed to examine chronicity of binge drinking (independent of chronic non-binge consumption) and whether there may be a specific threshold (i.e., number of binges) associated with the greatest level of CNS risk. Still, given evidence that binge drinking may be at least as

detrimental to the central nervous system as alcohol dependence, public safety measures that aim to reduce binge drinking behavior (including in social settings) may have widespread benefits, especially among older PWH.

While this study has strengths in novelty, use of a comprehensive neuropsychological battery, and clinical relevance, it also has several limitations. First, the HIV/Binge group-specific sample sizes were relatively small, particularly in Binge+ groups. Although this limited our ability to examine a full factorial three-way interaction between age, HIV status, and binge drinking status, we were still able to examine the novel age by HIV/Binge group interaction with adequate statistical power. Next, our assessment of binge drinking is based solely on self-report and may be subject to error by recall bias, memory difficulties, and/or social desirability bias; however, the majority of alcohol and substance use research relies on self-report of use. In addition, while binge drinking data specifically pertained to use within the last 30 days, we do not know exact amounts of time between participants' last binge episode and their participation in the study, limiting our ability to comment on how recency relates to cognitive performance. Future research may benefit from the use of more objective measures of alcohol use in daily life to more accurately characterize alcohol use patterns (e.g., a portable breathalyzer or wearable alcohol sensor). Finally, our exclusion of participants with current non-alcohol substance use disorders limits generalizability to others with binge drinking behavior and/or alcohol use disorder among whom polysubstance use is common.

In summary, the current study demonstrated detrimental additive (not synergistic) effects of HIV and binge drinking on neurocognitive functioning, and that older adults appear to be most vulnerable to these adverse effects particularly in the neurocognitive domains of learning, delayed recall, and motor skills. Our findings support the need for clinical screening for binge

drinking behavior given that many adults who engage in binge drinking behavior do not meet criteria for an AUD, as well as psychoeducation and psychosocial interventions targeting the reduction of binge drinking among older PWH. Additionally, given evidence that improvements in neurocognitive functioning may be possible after sustained sobriety following AUD recovery among HIV- populations (Stavro, Pelletier, & Potvin, 2013), future work is needed to understand whether this may also be true among PWH who reduce or cease binge drinking behavior.

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Table 1. Demographic and clinical characteristics by HIV/Binge groups

	A HIV-/Binge- (n=38)	B HIV-/Binge+ (n=23)	C HIV+/Binge- (n=55)	D HIV+/Binge+ (n=30)	*p*-value	Pairwise Differences
Demographics						
Age	35.50 (11.95)	41.43 (12.60)	46.42 (10.34)	43.87 (12.48)	**<0.001**	A < C,D
Education (years)	13.87 (2.61)	13.61 (2.62)	14.38 (2.41)	12.77 (2.76)	0.054	
Sex (male)	24 (63.2%)	16 (69.6%)	47 (85.5%)	27 (90.0%)	**0.017**	D > A,B
Race/ethnicity					0.319	
White	24 (63.2%)	10 (43.5%)	37 (67.3%)	14 (46.7%)		
Black	5 (13.2%)	2 (8.7%)	8 (14.6%)	4 (13.3%)		
Hispanic	7 (18.4%)	9 (39.1%)	9 (16.4%)	9 (30.0%)		
Other	2 (5.3%)	2 (8.7%)	1 (1.8%)	3 (10.0%)		
Psychiatric & Medical Characteristics						
Current MDD (yes)	1 (2.6%)	1 (4.3%)	2 (3.6%)	3 (10.0%)	0.706	
Lifetime MDD (yes)	12 (31.6%)	8 (34.8%)	26 (47.3%)	16 (53.3%)	0.577	
BDI-II score	6.41 (8.14)	6.09 (7.13)	9.48 (8.68)	9.79 (9.12)	0.151	
Hepatitis C (yes)	4 (10.5%)	1 (4.3%)	13 (23.6%)	6 (20.0%)	0.162	
Alcohol & Substance Use Characteristics						
Total days of alcohol use in the last 30 days	6 [1-8]	9 [3-24]	2 [1-4]	12 [4-18]	**<0.001**	B,D > A,C; A > C
Total alcohol drinks in the last 30 days	12 [4-26]	30 [14-131]	3 [1-9]	43 [13-107]	**<0.001**	B,D > A,C; A > C
Number of alcohol binges in the last 30 days	--	3 [1-7]	--	4 [1-10]	0.653	
Current AUD (yes)	0 (0.0%)	4 (17.4%)	1 (1.8%)	8 (26.7%)	**<0.001**	B,D > A,C
Lifetime AUD (yes)	5 (13.2%)	19 (82.6%)	15 (27.3%)	25 (83.3%)	**<0.001**	B,D > A,C
Lifetime total days of alcohol use	182 [34-943]	3770 [677-6085]	106 [12-1583]	2272 [822-6717]	**<0.001**	B,D > A,C
Lifetime total alcohol drinks	442 [103-3373]	22427 [1894-46877]	183 [14-5685]	13183 [2972-44140]	**<0.001**	B,D > A,C
Lifetime non-alcohol SUD (yes)	2 (5.3%)	9 (39.1%)	6 (10.9%)	15 (50.0%)	**<0.001**	B,D > A,C
HIV Disease Characteristics						
History of AIDS (yes)	--	--	30 (54.5%)	19 (63.3%)	0.432	
Nadir CD4	--	--	192 [70-276]	150 [44-275]	0.823	
Current CD4	--	--	462 [296-664]	593 [362-758]	0.285	
Estimated years living with HIV	--	--	12.64 (7.35)	13.12 (9.57)	0.800	
Plasma viral load (undetectable)	--	--	30 (58.8%)	20 (76.9%)	0.109	

Note. Values are mean (SD), n (%), or median [IQR]. Bolded *p*-values are significant at $p<0.05$. MDD = major depressive disorder; BDI-II = Beck Depression Inventory – Second Edition; AUD = alcohol use disorder; SUD = substance use disorder (including cannabis, cocaine, methamphetamine, opioids, sedatives, hallucinogens, and inhalants.

Table 2. Effect sizes and results of 2 x 2 factorial ANCOVA examining independent and interactive effects of HIV status and binge drinking status on neurocognitive T score outcomes that showed significant HIV/Binge group differences

Outcome: Global Cognition	F	p-value	η_p^2
HIV	**4.577**	**0.034**	**0.032**
Binge drinking	**9.129**	**0.003**	**0.062**
HIV * binge drinking	0.375	0.541	0.003
Total drinks in last 30 days	2.548	0.113	0.018
Age	**6.677**	**0.011**	**0.046**
Sex	0.020	0.888	0.000
Lifetime non-alcohol SUD	0.437	0.510	0.003
Outcome: Processing Speed			
HIV	**4.771**	**0.031**	**0.033**
Binge drinking	**6.770**	**0.010**	**0.047**
HIV * binge drinking	0.776	0.380	0.006
Total drinks in last 30 days	0.859	0.356	0.006
Age	**4.917**	**0.028**	**0.034**
Sex	0.157	0.692	0.001
Lifetime non-alcohol SUD	0.002	0.962	0.000
Outcome: Delayed Recall			
HIV	1.464	0.228	0.010
Binge drinking	**8.836**	**0.003**	**0.060**
HIV * binge drinking	0.001	0.979	0.000
Total drinks in last 30 days	1.233	0.269	0.009
Age	**17.316**	**<0.001**	**0.111**
Sex	0.033	0.857	0.000
Lifetime non-alcohol SUD	0.088	0.768	0.001
Outcome: Working Memory			
HIV	1.973	0.162	0.014
Binge drinking	**9.539**	**0.002**	**0.066**
HIV * binge drinking	0.222	0.638	0.002
Total drinks in last 30 days	1.489	0.224	0.011
Age	0.667	0.415	0.005
Sex	0.000	0.989	0.000
Lifetime non-alcohol SUD	1.744	0.189	0.013

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

Table 3. Multiple linear regression results examining independent and interactive effects of age and HIV/Binge group on global and domain-specific neurocognitive T score outcomes

	Global	Verbal Fluency	Executive Function	Processing Speed	Learning	Delayed Recall	Working Memory	Motor Skills
Age	-0.04 (0.09)	0.08 (0.12)	0.02 (0.14)	-0.17 (0.12)	-0.06 (0.12)	-0.05 (0.12)	-0.04 (0.13)	0.04 (0.15)
HIV-/Binge+ [a]	-2.82 (2.05)	-2.57 (2.60)	-5.08 (2.95)†	-1.72 (2.60)	-2.29 (2.70)	-5.04 (2.66)†	-4.43 (2.82)	0.99 (3.22)
HIV+/Binge- [a]	-1.72 (1.61)	-3.06 (2.03)	-2.80 (2.31)	-1.30 (2.03)	-1.09 (2.11)	-0.89 (2.08)	-1.66 (2.20)	0.16 (2.52)
HIV+/Binge+ [a]	-5.24 (1.99)**	-6.17 (2.49)*	-5.80 (2.83)*	-5.42 (2.50)*	-3.06 (2.59)	-4.66 (2.56)†	-8.05 (2.72)**	-3.03 (3.14)
Age * HIV-/Binge+ [a]	-0.13 (0.15)	0.01 (0.19)	-0.09 (0.22)	-0.06 (0.19)	-0.27 (0.20)	-0.11 (0.19)	-0.14 (0.21)	-0.32 (0.24)
Age * HIV+/Binge- [a]	-0.11 (0.13)	-0.03 (0.16)	-0.11 (0.19)	0.12 (0.16)	-0.23 (0.17)	-0.30 (0.17)†	-0.12 (0.18)	-0.35 (0.20)†
Age * HIV+/Binge+ [a]	-0.17 (0.14)	-0.10 (0.18)	-0.05 (0.20)	0.02 (0.18)	-0.37 (0.18)*	-0.42 (0.18)*	0.11 (0.19)	-0.66 (0.22)**
Total drinks in last 30 days	-0.01 (0.01)	0.01 (0.01)	-0.02 (0.01)	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01)	-0.01 (0.01	-0.01 (0.01)
Sex (female vs. male)	0.18 (1.43)	-1.59 (1.81)	0.38 (2.05)	0.18 (1.81)	0.49 (1.88)	0.59 (1.86)	-0.59 (1.97)	2.86 (2.25)
Lifetime non-alcohol SUD (yes vs. no)	0.89 (1.52)	1.35 (1.93)	2.91 (2.17)	0.35 (1.91)	-1.89 (1.99)	0.06 (1.96)	2.95 (2.11)	-2.96 (2.40)

Note. Values are regression estimate (SE).

[a]Compared to HIV-/Binge-

† $p<0.10$; * $p<0.05$; ** $p<0.01$

Figure 1. Mean differences in global and domain-specific neurocognitive T scores across HIV/Binge groups. *P*-values were derived from post-hoc Tukey HSD pairwise comparisons between the HIV-/Binge- and HIV+/Binge+ groups.

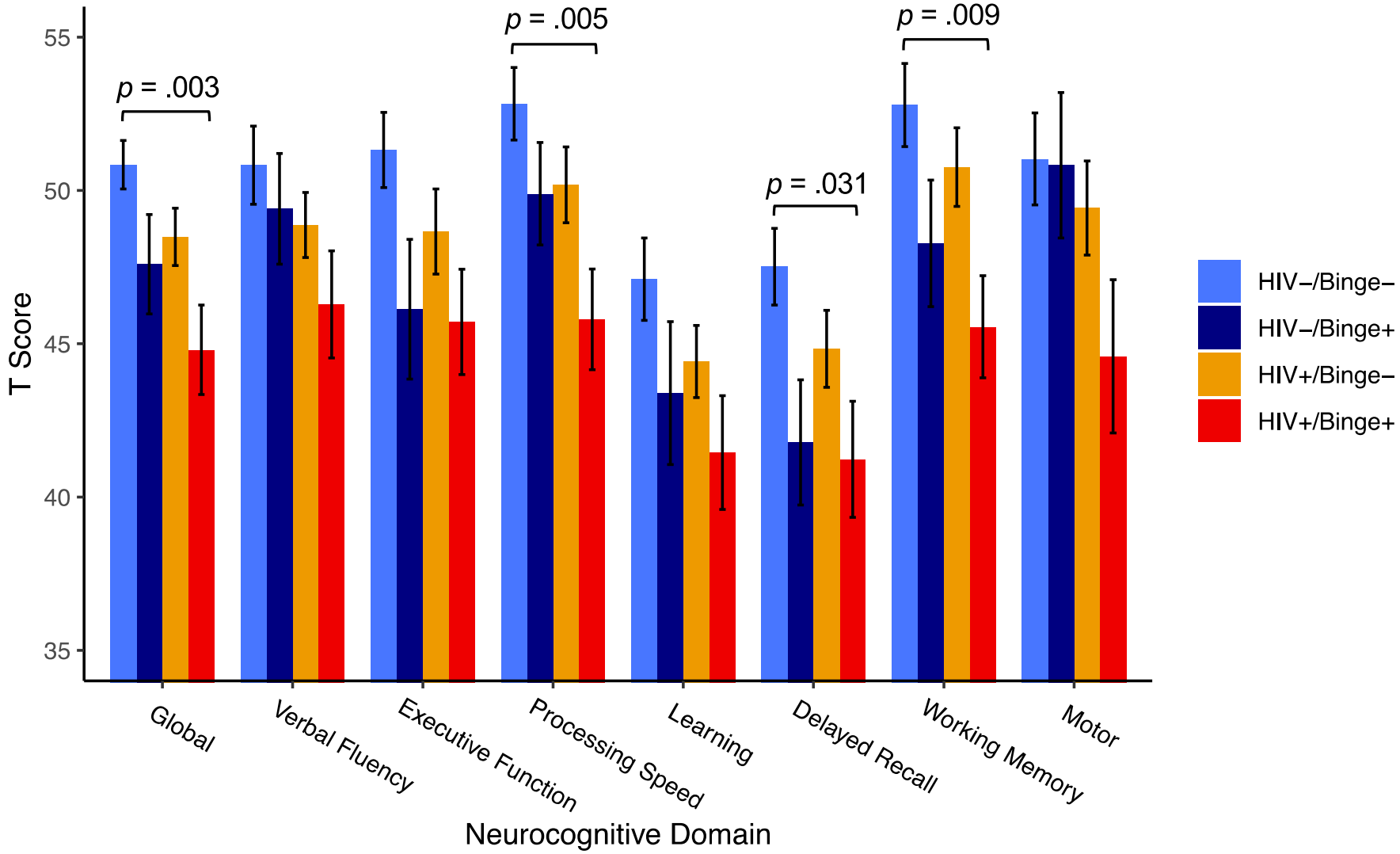

Figure 2. Differential associations between age and neurocognitive outcomes (i.e., learning, delayed recall, and motor skills) by HIV/Binge group.