UC San Diego
UC San Diego Previously Published Works

Title

Genetic variation in alcohol dehydrogenase is associated with neurocognition in men with HIV and history of alcohol use disorder: preliminary findings

Permalink

https://escholarship.org/uc/item/6rv697vb

Journal

Journal of NeuroVirology, 26(2)

ISSN

1355-0284

Authors

Saloner, Rowan

Paolillo, Emily W

Kohli, Maulika

et al.

Publication Date

2020-04-01

DOI

10.1007/s13365-019-00825-z

Peer reviewed

Genetic Variation in Alcohol Dehydrogenase is Associated with Neurocognition in Men with HIV and History of Alcohol Use Disorder: Preliminary Findings

Rowan Saloner, B.S.[1,2], **Emily W. Paolillo, M.S.**[1,2], **Maulika Kohli, B.A.**[1,2], **Sarah S. Murray, Ph.D.**[3], **David J. Moore, Ph.D.**[2], **Igor Grant, M.D.**[2], **Mariana Cherner, Ph.D.**[2]

[1]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, San Diego, California

[2]Department of Psychiatry, University of California San Diego, HIV Neurobehavioral Research Program, San Diego, California

[3]Department of Pathology, University of California San Diego, La Jolla, California

Abstract

The co-occurrence of HIV and alcohol use disorder (AUD) amplifies risk for neural injury and neurocognitive deficits. However, the substantial neurocognitive heterogeneity across HIV+/AUD+ individuals suggests inter-individual differences in vulnerability to the neurotoxicity of comorbid HIV/AUD. Genetic variation in alcohol dehydrogenase (ADH), which metabolizes ethanol, may contribute to inter-individual neurocognitive variability. We evaluated associations between five ADH single-nucleotide polymorphisms (SNPs) and neurocognition in men stratified by HIV and lifetime AUD status. Neurobehavioral assessments were administered to 153 men. Three-way ANOVAs examined the interaction of HIV, AUD, and ADH SNPs on global and domain-specific demographically-corrected T-scores. Follow-up ANCOVAs adjusted for age, estimated verbal IQ, depression, and remote non-alcohol substance use disorders. HIV/AUD groups differed globally and for verbal fluency, working memory, executive function, and processing speed T-scores specifically, with HIV+/AUD+ exhibiting the poorest performance. *ADH4* (rs1126671) was associated with large effects on working memory (d=−1.16, p=.001) and executive function (d=−0.77, p=.028) selectively in HIV+/AUD+, which remained significant in ANCOVA models. *ADH1A* (rs3819197) moderated the deleterious effects of HIV+/AUD+ on processing speed such that HIV+/AUD+ related to slower information processing in A-allele carriers but not GG homozygotes (ps<0.03). Preliminary findings suggest genetic variation in the ADH pathway moderates the deleterious neurocognitive effects of comorbid HIV/AUD. Differential metabolism of heavy ethanol exposure may compromise neurocognition under

Correspondence and Request for Reprints: Rowan Saloner, B.S., Predoctoral Research Fellow, SDSU/UC San Diego Joint Doctoral Program in Clinical Psychology, University of California, San Diego, HIV Neurobehavioral Research Program, 220 Dickinson Street, Suite B, Mail Code 8231, San Diego, CA 92103-8231, Phone: 619-543-5085, Fax: 619-543-1235, rsaloner@ucsd.edu.

conditions of neurobiological stress, such as in HIV infection. The functional effects on ethanol metabolism of ADH SNPs examined in this study remain poorly understood, warranting further examination of pharmacokinetic mechanisms mediating ADH gene-neurobehavior relationships in HIV.

Keywords

alcohol dehydrogenase; single nucleotide polymorphism; cognition; HIV-associated neurocognitive disorder; alcohol

INTRODUCTION

Heavy alcohol use is common among persons living with HIV (PLWH) and strongly linked to the transmission of HIV, higher viral replication, accelerated disease progression, and poorer disease management (Bryant, 2006; Galvan *et al*, 2002; Paolillo *et al*, 2017; Rehm *et al*, 2017). The combination of alcohol use disorder (AUD) and HIV infection compromises a host of biological functions, including hepatic, cardiovascular, and neurological systems (Molina *et al*, 2014; Price and Thio, 2010). Considering the multisystemic impact of chronic alcohol use and HIV, PLWH with comorbid AUDs are at an increased risk for frailty, lower health-related quality of life, and poorer everyday functioning (Blackstone *et al*, 2013; Justice *et al*, 2016; Rosenbloom *et al*, 2007).

The functional impairments and poor disease-related outcomes associated with heavy alcohol use in PLWH are partially driven by neurocognitive dysfunction (Heinz *et al*, 2014; Rothlind *et al*, 2005). Both AUD and HIV infection independently elevate risk for neurocognitive impairment; and within the context of HIV infection, heavy alcohol use is particularly detrimental to brain integrity and neurocognition (Cohen *et al*, 2019; Pfefferbaum *et al*, 2012; Rosenbloom *et al*, 2010). The pattern of neurocognitive deficits in HIV/AUD are predominantly attributed to frontal dysfunction, with specific involvement of frontostriatal (e.g., working memory, executive function, psychomotor speed) and frontoparietal (e.g., visuospatial, selective attention) circuits (Rosenbloom *et al*, 2010). Given that neurobehavioral dysfunction is a common consequence of comorbid HIV and AUD, examining the factors that moderate the relationship between HIV, AUD and neurocognition is warranted.

PLWH with heavy alcohol exposure are additionally burdened by biopsychosocial comorbidities (e.g., hepatitis C, depression, low socioeconomic status) that can obscure the detection of alcohol-specific mechanisms underlying neurocognitive dysfunction (Kennedy and Zerbo, 2014; Tedaldi *et al*, 2015). Indeed, alcohol use parameters do not reliably explain variance in neurocognitive performance in PLWH (Durvasula *et al*, 2001; Fama *et al*, 2009; Rothlind *et al*, 2005), suggesting the presence of inter-individual differences in neural vulnerability to heavy alcohol exposure. Although environmental factors have garnered the most attention, genetic predispositions that enhance alcohol-induced biological stress may also partially explain inter-individual differences in neurocognition among HIV/AUD populations.

One candidate mechanism occurring at the individual level is genetically-driven differences in the metabolism of alcohol (Hurley and Edenberg, 2012). Alcohol dehydrogenase (ADH) is the primary enzyme responsible for the conversion of ethanol into acetaldehyde, which is then oxidized into the less toxic acetate. The bulk of ethanol is metabolized by ADH in the liver, while the remainder of ethanol that reaches the CNS is metabolized by CYP2E1 and catalase (Hurley and Edenberg, 2012). ADH is encoded by several genes, and variation in these genes predicts level of alcohol consumption and risk of developing an AUD (Edenberg, 2007; Hurley and Edenberg, 2012). However, the extent to which ADH genetic variants moderate the effects of alcohol on other neurobehavioral phenotypes, including neurocognitive function, remains unclear. Moreover, genetically-driven differences in alcohol metabolism may be particularly salient in the context of HIV, in which PLWH have a diminished physiological capacity to combat the multi-system stressors induced by heavy alcohol exposure (Braithwaite *et al*, 2007).

Therefore, the present study examined associations between single-nucleotide polymorphisms (SNPs) in ADH genes and neurocognitive outcomes among participants stratified by HIV serostatus and lifetime AUD: HIV−/AUD−, HIV−/AUD+, HIV+/AUD−, and HIV+/AUD+. Based on prior research, we expected the HIV+/AUD+ group to demonstrate the poorest neurocognition. We hypothesized that ADH SNPs would exert effects on neurocognition only among AUD+ individuals (i.e., in the presence of substantial alcohol exposure), with the most pronounced effects occurring in the dual-risk HIV+/AUD+ group.

MATERIALS AND METHODS

Participants

This cross-sectional, retrospective study analyzed data from the baseline visit of 79 HIV-seropositive (HIV+) and 74 HIV-seronegative (HIV−) men enrolled in NIH-funded research studies at the University of California, San Diego's (UCSD) HIV Neurobehavioral Research Program (HNRP). Study visits took place between 2002 and 2012. All participants gave written informed consent as approved by the UCSD Institutional Review Board. For the present analysis, exclusion criteria were: 1) DSM-IV criteria for substance use dependence for any drugs other than alcohol and cannabis within the last 5 years, alcohol dependence within the past 12 months, or abuse of any substances other than alcohol and cannabis within the last 12 months; 2) diagnosis of psychotic or mood disorder with psychotic features, neurological, or medical condition that may impair neurocognitive functioning, such as traumatic brain injury, stroke, epilepsy, or advanced liver disease; 3) low verbal IQ of < 70 as estimated by the Fourth edition of the reading subtest of the Wide Range Achievement Test (WRAT-IV; (Wilkinson and Robertson, 2006); 4) evidence of intoxication by illicit drugs (except marijuana) by positive urine toxicology or positive Breathalyzer test for alcohol on the day of testing; and 5) being female. We restricted our sample to men because ADH activity is known to differ by gender (Thomasson, 1995) and there were insufficient numbers of women participants in the parent studies to support separate analyses. With the exception of HIV serostatus and lifetime AUD, exclusion criteria were identical for all four HIV/AUD groups.

Alcohol, Substance Use, and Psychiatric Evaluation

Participants were evaluated for current and past mood and substance use disorders using structured interviews conforming to DSM-IV criteria, as study methodology was developed prior to the release of the DSM-5. Diagnoses were made with the Structured Clinical Interview for DSM-IV (SCID-IV; (Spitzer *et al*, 1995) or the Composite International Diagnostic Interview (CIDI; (World Health Organization, 1998). To align with current DSM-5 criteria, AUD was defined as a DSM-IV lifetime diagnosis of alcohol abuse or dependence. DSM-IV criteria for alcohol abuse is met when participants endorse recurring problems (e.g., interpersonal, work-related, legal) stemming from sustained alcohol use. DSM-IV criteria for alcohol dependence is met when participants report symptoms of tolerance, withdrawal, and impaired control over drinking. For the present study, participants were stratified into four groups based on HIV serostatus and lifetime AUD: HIV−/AUD− (n = 45), HIV−/AUD+ (n = 29), HIV+/AUD− (n = 45), HIV+/AUD+ (n = 34). Of the 63 AUD+ participants, four HIV− and two HIV+ individuals met criteria for a current (30-day) AUD (abuse only). A semi-structured timeline follow-back interview was administered to gather a detailed history of quantity, frequency, and duration of alcohol exposure over a participant's lifetime. Current affective distress was assessed using the Beck Depression Inventory-II (BDI-II; (Beck *et al*, 1996)).

Neuromedical Assessment

All participants underwent a comprehensive neuromedical assessment and blood draw. HIV serological status was diagnosed by enzyme-linked immunosorbent assay (ELISA) with Western blot confirmation. Hepatitis C co-infection was determined to be present only in HIV+ individuals; however, this prevalence was infrequent and HIV/AUD groups did not differ significantly with regard to hepatitis C seropositivity. Current CD4+ T-cell counts were measured in blood by routine clinical flow cytometry. 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 [LLQ] of 50 copies/ml. HIV viral load was considered undetectable below the LLQ of 50 copies/ml.

Neurocognitive Assessment

Participants completed a standardized battery of neurocognitive tests designed to provide a comprehensive assessment of neurocognitive domains most impacted in HIV and AUD: verbal fluency, executive function, processing speed, learning, delayed recall, working memory, and motor skills (Heaton *et al*, 2010). Raw test scores were converted to demographically-corrected standard T scores (mean of 50 and standard deviation of 10) that adjusted for the effects of age, education, sex and race/ethnicity, as appropriate (Heaton *et al*, 2004; Heaton *et al*, 2003; Norman *et al*, 2011). The demographically-corrected T scores were averaged across all tests to derive a global mean T score, and averaged within each neurocognitive ability area to create domain-specific T scores. These global and domain-specific T scores were used as outcomes in analyses.

ADH4 Genotyping

DNA for genotyping was isolated from stored whole blood or peripheral blood mononuclear cells (PBMCs) using the Qiagen QIAamp DNA Mini Kit (Qiagen, Valencia, CA). ADH SNPs were assayed using an array designed by NIAAA focused on SNPs with relevance to addictions (Hodgkinson *et al*, 2008), using the Illumina BeadStation genotyping platform and GoldenGate genotyping assay.

The distribution of the five ADH SNPs included for analysis are presented in Table 1. All SNP distributions were consistent with Hardy-Weinberg equilibrium. The sample size for minor allele homozygotes was small for each SNP; thus, each ADH SNP was coded according to a recessive genetic model such that heterozygotes and minor allele homozygotes were grouped together in comparison to major allele homozygotes. SNPs that were rare or had low cell rates (i.e., n < 10 per cell) were excluded from analyses.

Although it is established that ADH polymorphisms are linked to different levels of alcohol metabolism, there is limited knowledge on the directionality of metabolic effects for the ADH SNPs examined in the current study. Moreover, the frequent co-occurrence of SNPs (i.e., high linkage disequilibrium) within and between ADH genes makes it difficult to isolate our results to SNP-specific mechanisms (Hurley and Edenberg, 2012), particularly in the context of a candidate gene study with limited genotyping data. Therefore, our interpretation of ADH SNP analyses places a greater emphasis on genetically-driven variation in alcohol metabolism than ADH SNP-specific pathways.

Statistical Analysis

HIV/AUD group differences in demographics, alcohol use parameters, neuropsychiatric and HIV disease characteristics, and neurocognitive T scores were examined using analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables and Chi-square statistics for categorical variables. To follow-up on significant omnibus results, pair-wise comparisons were conducted using Tukey's Honest Significant Difference (HSD) tests for continuous outcomes or Bonferroni-corrections for categorical outcomes. In the full study sample, the same univariate comparisons were conducted for ADH SNPs. Cohen's *d* statistics are presented for estimates of effect size for pair-wise comparisons.

For each SNP, separate three-way ANOVAs (HIV × AUD × SNP) were conducted to examine whether ADH genetic variation moderated the effects of HIV/AUD status on neurocognitive outcomes. These analyses were restricted to neurocognitive outcomes that displayed at least a trend-level univariate association ($p < 0.10$) with HIV/AUD status. We employed the Benjamini-Hochberg procedure to correct for multiple comparisons by controlling for the false discovery rate within each set of SNP-specific ANOVAs (Benjamini and Hochberg, 1995). For each ANOVA that yielded a significant three-way interaction effect ($p < .05$), a follow-up ANCOVA was conducted to examine potential attenuation of interaction effects after covarying for estimated premorbid verbal IQ, as measured by the WRAT-IV, and clinical characteristics that significantly differed by HIV/AUD or SNP groups. *A priori* planned comparisons were conducted by examining ADH SNP group

differences in neurocognitive outcomes within each HIV/AUD group, as well as pairwise HIV/AUD group differences within SNP groups.

As a follow-up analysis for HIV+ individuals, HIV disease and treatment characteristics known to be related to neurocognitive function in the era of antiretroviral therapy (ART; i.e., nadir CD4, current CD4, HIV plasma viral load detectability, and ART status [on/off]; (Heaton *et al*, 2010), were added as additional covariates to 2×2 ANCOVAs (AUD × SNP) to examine potential HIV-related attenuation of the effect of ADH SNPs. All analyses were performed using JMP Pro version 14.0.0 (JMP®, Version <14.0.0>. SAS Institute Inc., Cary, NC, 2018).

RESULTS

Participant Characteristics

Participant characteristics by HIV/AUD group are presented in Table 2. Groups were comparable with respect to years of education, WRAT-IV scores, and race/ethnicity. However, the HIV+/AUD+ group was significantly older than the HIV−/AUD− group (42.5 vs. 34.8; $p = .02$). As expected, both AUD+ groups (HIV−/AUD+ and HIV+/AUD+) reported the highest lifetime exposure to alcohol, as evidenced by significantly more lifetime drinks, lifetime drinking days, and lifetime average drinks per drinking day than both AUD− groups (HIV−/AUD− and HIV+/AUD−). HIV−/AUD− participants reported more lifetime average drinks per drinking day than HIV+/AUD− participants (3.23 vs. 2.51; $p = .04$). HIV/AUD groups did not differ with respect to age of first drink and days since last drink. HIV+ groups had higher rates of lifetime and current Major Depressive Disorder (MDD) and higher BDI-II scores than HIV− groups. Although HIV/AUD groups significantly differed at the omnibus level with respect to rates of lifetime non-alcohol substance use disorder, with AUD+ groups displaying higher rates than AUD− groups, there were no significant pair-wise differences. The two HIV+ groups did not significantly differ with respect to HIV disease characteristics.

Neurocognition Across HIV/AUD Groups

Global and domain-specific neurocognitive T scores for each HIV/AUD group are displayed in Figure 1. Significant omnibus group differences were detected for global functioning ($F = 3.25$, $p = .024$), verbal fluency ($F = 3.40$, $p = .019$), and working memory ($F = 2.72$; $p = .046$) T scores. Tukey's HSD tests indicated that HIV+/AUD+ participants had significantly poorer global ($d = −.72$; $p = .030$) and verbal fluency ($d = −.67$; $p = .029$) T scores than the HIV−/AUD− participants. Trend-level omnibus group differences were also detected for executive function ($F = 2.26$, $p = .084$) and processing speed ($F = 2.26$, $p = .084$) T scores.

ADH Genotypes and Neurocognition in the Context of HIV and AUD

Three-way ANOVAs examining the interaction effects of HIV serostatus (HIV+ vs. HIV−), AUD status (AUD+ vs. AUD−), and ADH SNPs (major allele homozygous vs. [heterozygous and minor allele homozygous]) were conducted for neurocognitive outcomes that showed significant differences or trends toward significance across HIV/AUD groups:

global, verbal fluency, working memory, executive function, and processing speed. Models with significant three-way interaction effects are reported in Table 3. Results indicated significant HIV × AUD × *ADH4* (rs1126671) effects for executive function ($F = 7.38$, $p = 0.007$, $\eta_p^2 = 0.05$) and working memory ($F = 5.58$, $p = 0.020$, $\eta_p^2 = 0.04$), as well as a trend-level three-way interaction for global functioning ($F = 3.03$, $p = 0.084$, $\eta_p^2 = 0.02$). The three-way interaction effects for executive function and working memory remained significant after controlling for the false discovery rate. Follow-up comparisons for executive function and working memory revealed significant *ADH4* (rs1126671) differences in neurocognition only within the HIV+/AUD+ group (see Figure 2), with *ADH4* (rs1126671) GG homozygotes displaying poorer executive function ($d = -0.77$, $p = .028$) and working memory ($d = -1.16$, $p = .001$) than A allele carriers. In *ADH4* (rs1126671) GG homozygotes, pairwise comparison tests indicated significantly poorer neurocognition in HIV+/AUD+ participants compared to HIV−/AUD− (executive function: $d = -0.70$, $p = .045$; working memory: $d = -1.04$, $p = .003$), HIV+/AUD− (executive function: $d = -1.02$, $p = .003$; working memory: $d = -0.77$, $p = .024$), and HIV−/AUD+ (executive function: $d = -1.13$, $p = .002$; working memory: $d = -1.04$, $p = .011$). *ADH4* (rs1126671) GG homozygote pairwise comparisons between HIV−/AUD−, HIV+/AUD−, and HIV−/AUD+ did not reach significance. Similarly, analyses within *ADH4* (rs1126671) A allele carriers did not reveal any significant pairwise differences between the four HIV/AUD groups.

Results also indicated an HIV × AUD × *ADH1A* (rs3819197) interaction effect for processing speed ($F = 4.66$, $p = 0.033$, $\eta_p^2 = 0.03$). In *ADH1A* (rs3819197) A allele carriers, pairwise comparison tests indicated significantly poorer processing speed in HIV+/AUD+ participants compared to HIV−/AUD− ($d = -0.87$, $p = .020$), HIV+/AUD− ($d = -0.85$, $p = .019$), and HIV−/AUD+ ($d = -0.88$, $p = .029$). In *ADH1A* (rs3819197) GG homozygotes, pairwise HIV/AUD comparison tests indicated significantly poorer processing speed in HIV+/AUD− participants compared to HIV−/AUD− ($d = -0.65$, $p = .025$). Within HIV/AUD groups, *ADH1A* (rs3819197) group differences in processing speed did not reach statistical significance. The three-way interaction effect for HIV × AUD × *ADH1A* (rs3819197) on processing speed did not remain statistically significant after controlling for the false discovery rate. Although not statistically significant, results also indicated several trend-level three-way interactions involving *ADH7* SNPs. Specifically, trend-level effects were detected for HIV × AUD × *ADH7* (rs894369) on working memory ($F = 2.79$, $p = 0.097$, $\eta_p^2 = 0.02$) and HIV × AUD × *ADH7* (rs1154470) on executive function ($F = 2.79$, $p = 0.097$, $\eta_p^2 = 0.02$) and working memory ($F = 2.79$, $p = 0.097$, $\eta_p^2 = 0.02$).

Adjusted Models Controlling for Clinical Factors

ANCOVA models (see Table 3) were conducted to determine whether the significant interaction effects of HIV, AUD, and *ADH4* [rs1126671] on neurocognition were attenuated by estimated premorbid function (i.e., WRAT-IV) and clinical factors that significantly differed across HIV/AUD groups (i.e., age, lifetime MDD, BDI-II, and lifetime non-alcohol substance use disorders). The only ADH SNP group difference in clinical characteristics occurred across *ADH1A* groups, in which A allele carriers exhibited significantly higher lifetime rates of other (non-alcohol) substance use disorders than *ADH1A* GG homozygotes

(44% vs. 23%; $p = .007$). Thus, no additional covariates were added to ANCOVA models. In these adjusted models, the HIV × AUD × *ADH4* (rs1162271) interaction remained significantly associated with executive function ($p = .019$) and working memory ($p = .049$). Higher WRAT-IV scores were significantly associated with higher executive function ($F = 12.70$, $p = 0.001$, $\eta_p^2 = 0.08$) and working memory ($F = 6.72$, $p = 0.011$, $\eta_p^2 = 0.05$), while individuals with a lifetime diagnosis of MDD had significantly lower executive function ($F = 10.736$, $p = 0.002$, $\eta_p^2 = 0.07$) and working memory T scores ($F = 4.56$, $p = 0.034$, $\eta_p^2 = 0.03$) compared to those without a lifetime diagnosis of MDD.

Relationships In HIV+ Individuals

For the significant HIV × AUD × *ADH4* (rs1162271) ANCOVA models, subset analyses in HIV+ participants (AUD × *ADH4* [rs116227]) were conducted to control for nadir and current CD4 counts, ART status, and HIV plasma viral load detectability. The interaction effect between AUD and *ADH4* (rs116227) was significant for working memory ($p = .027$) and at trend-level significance for executive function ($p = .096$). None of the HIV-specific variables significantly contributed to neurocognitive performance. WRAT-IV scores remained a significant predictor of executive function and working memory, while lifetime MDD remained a significant predictor of executive function.

DISCUSSION

To our knowledge, this preliminary study is the first to examine associations between SNPs coding for alcohol metabolism and neurocognition in the context of HIV infection and AUD. As expected, HIV+/AUD+ participants exhibited the poorest neurocognitive performance among the four study groups. Our findings demonstrate that genetic variation in the ADH pathway moderates the deleterious neurocognitive effects of comorbid HIV infection and AUD, particularly in higher-order skills (i.e., executive function, working memory) supported by prefrontal brain regions. Contrary to expectations, ADH SNPs did not relate to neurocognition among HIV−/AUD+ participants, suggesting that differential metabolism of heavy ethanol exposure may be most salient under conditions of high neurobiological stress, such as HIV-related neurotoxicity.

The strongest SNP associations occurred with the *ADH4* (rs1126671) SNP, for which significant SNP effects on executive function and working memory only emerged under the dual-risk condition of comorbid HIV infection and AUD. Despite limited power due to small sample size, these effects were fairly robust to psychosocial and HIV-specific factors. The ADH4 enzyme contributes to roughly 30% of the ethanol oxidizing capacity in the liver during high ethanol concentrations (Cederbaum, 2012; Edenberg *et al*, 2006). Compared to the A allele, the G allele of the *ADH4* rs1126671 SNP reduces the thermostability and ethanol-binding of ADH4 (referred to as ADH2 by Strömberg et al.; (Edenberg *et al*, 2006; Strömberg *et al*, 2002). This G allele-associated reduction in stability could underlie the neurocognitive deficits observed among HIV+/AUD+ GG homozygotes, however, it is unclear whether these thermokinetic differences translate to functional differences in ethanol metabolism.

Mechanisms underlying the relationships between ADH genetic variability, alcohol metabolism, and neurocognitive outcomes are not well understood. Moreover, the specific neurotoxic effects of ethanol versus its first metabolite, acetaldehyde, are also understudied; however, both seem to have potentially detrimental effects on brain function. Consistent evidence suggests that ethanol may have direct and indirect effects on neuronal damage via oxidative and inflammatory mechanisms (Alfonso-Loeches *et al*, 2010; Sun and Sun, 2001). ADH variants that cause decreased alcohol metabolism in the liver lead to increased bioavailability of ethanol throughout the body, including the brain, where it is then metabolized primarily by CYP2E1. This within-brain metabolic process has been shown to increase production of reactive oxygen species (ROS) and nitric oxide, promoting oxidative- and inflammation-related neurodegeneration (Haorah *et al*, 2008). Our results demonstrating that PLWH are selectively impacted by the neurocognitive effects of ADH genes is supported by evidence that ethanol metabolism is altered in HIV disease, and that ADH can modulate ART pharmacokinetics to heighten the risk of liver toxicity (Haorah *et al*, 2004; Pandrea *et al*, 2010).

ADH variants that cause increased alcohol metabolism in the liver lead to decreased bioavailability of ethanol and increased acetaldehyde accumulation. The direct effects of acetaldehyde on neuronal injury, however, are less clear, as much of the research on acetaldehyde has focused on its carcinogenic and psychologically reinforcing properties (Foddai *et al*, 2004; Seitz and Stickel, 2010). It is also difficult to disentangle neurotoxic effects that result from the process of within-brain ethanol metabolism versus the simple presence of acetaldehyde in the CNS. Some research suggests acetaldehyde is cytotoxic (much more so than ethanol) via pathways that inhibit astrocyte viability and proliferation (Sarc and Lipnik-Stangelj, 2009). Indirectly, acetaldehyde can also cause downstream detrimental effects on brain integrity via multi-organ damage in the periphery (e.g., hepatic encephalopathy; (Butterworth, 2014). Although not statistically significant, a greater percentage of the HIV+AUD group (17.6%) relative to the HIV only group (6.7%) had HCV co-infection, which has been linked to higher concentrations of ADH and presumably increased production of acetaldehyde (Jelski *et al*, 2016; Jelski *et al*, 2018).

The current study demonstrated neurocognitive domain-specific findings primarily in executive function and working memory. This suggests that genetically-driven differential metabolism of alcohol preferentially involves the prefrontal cortex, and is consistent with known vulnerabilities among individuals with HIV and/or AUD (Rosenbloom *et al*, 2010). Translational research suggests that mechanisms underlying the dysfunction of prefrontal-mediated cognitive domains in both HIV and AUD likely include disruption of the dopaminergic system. Chronic alcohol exposure appears to disrupt dopaminergic neurotransmission by reducing dopamine receptor activity and dopamine transporter availability, which have consistently shown to be associated with executive dysfunction (Narendran *et al*, 2014; Trantham-Davidson *et al*, 2014; Trantham-Davidson *et al*, 2017; Trantham-Davidson and Chandler, 2015; Yen *et al*, 2015). HIV is also neurotoxic to dopaminergic neurons, as viral proteins (e.g., Tat, gp120) cause excitotoxicity and cell death within frontostriatal circuitry (Gaskill *et al*, 2017; Koutsilieri *et al*, 2001). HIV-related dopamine dysfunction has been directly linked to neurocognitive deficits (Kumar *et al*, 2011), and the deleterious neurocognitive effects of HIV appear to be heightened when

coupled with genetic risk for low dopamine bioavailability (Saloner *et al*, 2019; Sundermann *et al*, 2015). Last, we also found an interaction effect on processing speed. This domain-specific finding is also consistent with prior work on neurocognitive outcomes in comorbid HIV and AUD, as injury to white matter is common in both conditions (Paolillo *et al*, 2019; Rosenbloom *et al*, 2010). Notably, the processing speed finding was not significant after correction for multiple comparisons.

Psychosocial factors can be a principal source of cognitive reserve among adults with risks for cognitive deficits, including HIV and/or AUD (Malaspina *et al*, 2011; Vance, 2013). In our sample, we found that higher estimated verbal IQ (WRAT-IV Reading) and absence of lifetime MDD significantly predicted better neurocognitive outcomes. These findings are very consistent with previous research in this population. WRAT-IV Reading score is primarily used as an indicator of premorbid ability, can be used to estimate education quality, and is known to be strongly correlated to neurocognitive performance across clinical and non-clinical populations (Foley *et al*, 2012; Opdebeeck *et al*, 2016). Depression has been found to have both transient and longstanding effects on neurocognitive performance across several domains, including processing speed, memory, and executive functioning (McDermott and Ebmeier, 2009). For example, neurocognitive deficits are commonly seen during acute depressive episodes, though performance can improve somewhat after the episode resolves (Douglas and Porter, 2009). Additional research also suggests that a history of chronic MDD also exerts long-term effects on neurocognitive functioning via chronic stress-induced inflammatory neuronal damage (Wolkowitz *et al*, 2010). Future work to inform this area of "psychosocial reserve" should examine possible interactive effects with genetics on neurocognition in HIV and AUD.

The current investigation is not without limitations. For a gene-behavior study, our sample size was small and our results should be considered preliminary. Although grouping SNPs according to a recessive genetic model (i.e., minor allele carriers vs. major allele homozygotes) is common practice, our findings need to be replicated in larger samples that have sufficient power to treat each allelic variant independently. Despite our small sample size with limited power, we still detected large effects that remained statistically significant after adjusting for relevant covariates. Our examination of SNPs involved in the ADH pathway highlights the influence of genetic variation in alcohol metabolism as a protective/risk factor for neurobehavioral dysfunction in HIV+/AUD+ individuals; however, in this retrospective study we did not have phenotypic data on the functional effect of the ADH SNPs on actual alcohol metabolism. Future mechanistic research should continue to examine how ADH enzymatic activity differs among ADH variants, and how these genotype-phenotype relationships are modulated by environmental conditions such as HIV infection and chronic alcohol exposure. Although our inclusion of genetic factors somewhat mitigates the shortcomings of our cross-sectional and associative analysis, it is not possible for us to determine the directionality of the relationships between HIV/AUD status and neurocognition. Prefrontal dysfunction may serve as both an antecedent and consequence of HIV infection and problematic alcohol use (Day *et al*, 2015; Gierski *et al*, 2013; Ross *et al*, 2016; Walker and Brown, 2018), which underscores the relevance of identifying genetic risk factors that exacerbate HIV– and alcohol-related neurocognitive vulnerabilities. Lastly, our sample comprised only men and we are therefore limited in extrapolating our findings to

women. Replication studies in women are warranted considering that in addition to alcohol metabolism, the neurocognitive effects of HIV and AUD may differ by sex (Sharrett-Field *et al*, 2013; Sundermann *et al*, 2018).

Taken together, our preliminary findings indicate a context-dependent relationship between alcohol metabolism genetics and neurocognition, such that ADH SNPs were related to neurocognition only under the environmental conditions of AUD and HIV infection. Our domain-specific analyses align with the hallmark neurocognitive deficits of HIV+/AUD+ individuals as our significant ADH genetics findings were circumscribed to executive function, working memory, and to a lesser extent, processing speed. Replication and examination of pharmacokinetic mechanisms mediating the relationship between ADH genetics and neurobehavioral outcomes may inform precision treatments for chronic drinkers living with HIV and help to identify patients that are particularly susceptible to the deleterious neurocognitive effects of HIV infection and AUD.

ACKNOWLEDGMENTS

REFERENCES

Alfonso-Loeches S, Pascual-Lucas M, Blanco AM, Sanchez-Vera I, Guerri C (2010). Pivotal role of TLR4 receptors in alcohol-induced neuroinflammation and brain damage. J Neurosci 30: 8285–95. [PubMed: 20554880]

Beck A, Steer R, Brown G (1996). Manual for Beck Depression Inventory II (BDI-II). San Antonio, TX, Psychology Corporation.

Benjamini Y, Hochberg Y (1995). Controlling the false discovery rate: a practical and powerful approach to multiple testing. Journal of the Royal statistical society: series B (Methodological) 57: 289–300.

Blackstone K, Iudicello JE, Morgan EE, Weber E, Moore DJ, Franklin DR, Ellis RJ, Grant I, Woods SP (2013). Human immunodeficiency virus infection heightens concurrent risk of functional dependence in persons with long-term methamphetamine use. J Addict Med 7: 255–63. [PubMed: 23648641]

Braithwaite RS, Conigliaro J, Roberts MS, Shechter S, Schaefer A, McGinnis K, Rodriguez MC, Rabeneck L, Bryant K, Justice AC (2007). Estimating the impact of alcohol consumption on survival for HIV+ individuals. AIDS Care 19: 459–66. [PubMed: 17453583]

Bryant KJ (2006). Expanding research on the role of alcohol consumption and related risks in the prevention and treatment of HIV/AIDS. Subst Use Misuse 41: 1465–507. [PubMed: 17002990]

Butterworth RF (2014). Hepatic encephalopathy in alcoholic cirrhosis. Handb Clin Neurol 125: 589–602. [PubMed: 25307598]

Cederbaum AI (2012). Alcohol metabolism. Clin Liver Dis 16: 667–85. [PubMed: 23101976]

Cohen RA, Gullett JM, Porges EC, Woods AJ, Lamb DG, Bryant VE, McAdams M, Tashima K, Cook R, Bryant K (2019). Heavy Alcohol Use and Age Effects on HIV-Associated Neurocognitive Function. Alcoholism: Clinical and Experimental Research 43: 147–157.

Day AM, Kahler CW, Ahern DC, Clark US (2015). Executive Functioning in Alcohol Use Studies: A Brief Review of Findings and Challenges in Assessment. Curr Drug Abuse Rev 8: 26–40. [PubMed: 25877524]

Douglas KM, Porter RJ (2009). Longitudinal assessment of neuropsychological function in major depression. Aust N Z J Psychiatry 43: 1105–17. [PubMed: 20001409]

Durvasula RS, Miller EN, Myers HF, Wyatt GE (2001). Predictors of Neuropsychological Performance in HIV Positive Women. Journal of Clinical and Experimental Neuropsychology 23: 149–163. [PubMed: 11309669]

Edenberg HJ (2007). The genetics of alcohol metabolism: role of alcohol dehydrogenase and aldehyde dehydrogenase variants. Alcohol Res Health 30: 5–13. [PubMed: 17718394]

Edenberg HJ, Xuei X, Chen H, Tian H, Wetherill LF, Dick DM, Almasy L, Bierut L, Bucholz KK, Goate A, Hesselbrock V, Kuperman S, Nurnberger J, Porjesz B, Rice J, Schuckit M, Tischfield J, Begleiter H, Foroud T (2006). Association of alcohol dehydrogenase genes with alcohol dependence: a comprehensive analysis. Human Molecular Genetics 15: 1539–1549. [PubMed: 16571603]

Fama R, Rosenbloom MJ, Nichols BN, Pfefferbaum A, Sullivan EV (2009). Working and episodic memory in HIV infection, alcoholism, and their comorbidity: baseline and 1-year follow-up examinations. Alcohol Clin Exp Res 33: 1815–24. [PubMed: 19656122]

Foddai M, Dosia G, Spiga S, Diana M (2004). Acetaldehyde increases dopaminergic neuronal activity in the VTA. Neuropsychopharmacology 29: 530–6. [PubMed: 14973432]

Foley JM, Ettenhofer ML, Kim MS, Behdin N, Castellon SA, Hinkin CH (2012). Cognitive reserve as a protective factor in older HIV-positive patients at risk for cognitive decline. Appl Neuropsychol Adult 19: 16–25. [PubMed: 22385375]

Galvan FH, Bing EG, Fleishman JA, London AS, Caetano R, Burnam MA, Longshore D, Morton SC, Orlando M, Shapiro M (2002). The prevalence of alcohol consumption and heavy drinking among people with HIV in the United States: results from the HIV Cost and Services Utilization Study. J Stud Alcohol 63: 179–86. [PubMed: 12033694]

Gaskill PJ, Miller DR, Gamble-George J, Yano H, Khoshbouei H (2017). HIV, Tat and dopamine transmission. Neurobiol Dis 105: 51–73. [PubMed: 28457951]

Gierski F, Hubsch B, Stefaniak N, Benzerouk F, Cuervo-Lombard C, Bera-Potelle C, Cohen R, Kahn JP, Limosin F (2013). Executive functions in adult offspring of alcohol-dependent probands: toward a cognitive endophenotype? Alcohol Clin Exp Res 37 Suppl 1: E356–63. [PubMed: 23240659]

Haorah J, Heilman D, Diekmann C, Osna N, Donohue TM Jr., Ghorpade A, Persidsky Y (2004). Alcohol and HIV decrease proteasome and immunoproteasome function in macrophages: implications for impaired immune function during disease. Cell Immunol 229: 139–48. [PubMed: 15474528]

Haorah J, Ramirez SH, Floreani N, Gorantla S, Morsey B, Persidsky Y (2008). Mechanism of alcohol-induced oxidative stress and neuronal injury. Free Radic Biol Med 45: 1542–50. [PubMed: 18845238]

Heaton RK, Clifford DB, Franklin DR Jr., Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology 75: 2087–96. [PubMed: 21135382]

Heaton RK, Miller SW, Taylor MJ, Grant I (2004). Revised Comprehensive Norms for an Expanded Halstead Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Psychological Assessment Resources, Inc: Lutz, FL.

Heaton RK, Taylor MJ, Manly J (2003). Demographic effects and use of demographically corrected norms with the WAIS-III and WMS-III In: Clinical interpretation of the WAIS-III and WMS-III. Academic Press: San Diego, CA, US, pp 181–210.

Heinz AJ, Fogler KA, Newcomb ME, Trafton JA, Bonn-Miller MO (2014). Problematic alcohol use among individuals with HIV: relations with everyday memory functioning and HIV symptom severity. AIDS Behav 18: 1302–14. [PubMed: 23979498]

Hodgkinson CA, Yuan Q, Xu K, Shen PH, Heinz E, Lobos EA, Binder EB, Cubells J, Ehlers CL, Gelernter J, Mann J, Riley B, Roy A, Tabakoff B, Todd RD, Zhou Z, Goldman D (2008). Addictions biology: haplotype-based analysis for 130 candidate genes on a single array. Alcohol Alcohol 43: 505–15. [PubMed: 18477577]

Hurley TD, Edenberg HJ (2012). Genes encoding enzymes involved in ethanol metabolism. Alcohol Res 34: 339–44. [PubMed: 23134050]

Jelski W, Strumnik A, Orywal K, Lapinski TW, Swiderska M, Szmitkowski M (2016). Serum Alcohol Dehydrogenase and Aldehyde Dehydrogenase Activity in the Course of Hepatitis C. Clin Lab 62: 2155–2159. [PubMed: 28164655]

Jelski W, Strumnik A, Orywal K, Lapinski TW, Swiderska M, Szmitkowski M (2018). Activity of alcohol dehydrogenase isoenzymes and aldehyde dehydrogenase in sera of patients with hepatitis C. Arch Med Sci 14: 281–287. [PubMed: 29593800]

Justice AC, McGinnis KA, Tate JP, Braithwaite RS, Bryant KJ, Cook RL, Edelman EJ, Fiellin LE, Freiberg MS, Gordon AJ, Kraemer KL, Marshall BD, Williams EC, Fiellin DA (2016). Risk of mortality and physiologic injury evident with lower alcohol exposure among HIV infected compared with uninfected men. Drug Alcohol Depend 161: 95–103. [PubMed: 26861883]

Kennedy CA, Zerbo E (2014). HIV-Related Neurocognitive Disorders and Drugs of Abuse: Mired in Confound, Surrounded by Risk. Current Addiction Reports 1: 229–236.

Koutsilieri E, ter Meulen V, Riederer P (2001). Neurotransmission in HIV associated dementia: a short review. J Neural Transm (Vienna) 108: 767–75. [PubMed: 11478426]

Kumar AM, Ownby RL, Waldrop-Valverde D, Fernandez B, Kumar M (2011). Human immunodeficiency virus infection in the CNS and decreased dopamine availability: relationship with neuropsychological performance. J Neurovirol 17: 26–40. [PubMed: 21165787]

Malaspina L, Woods SP, Moore DJ, Depp C, Letendre SL, Jeste D, Grant I, Group HIVNRP (2011). Successful cognitive aging in persons living with HIV infection. J Neurovirol 17: 110–9. [PubMed: 21165783]

McDermott LM, Ebmeier KP (2009). A meta-analysis of depression severity and cognitive function. J Affect Disord 119: 1–8. [PubMed: 19428120]

Molina PE, Bagby GJ, Nelson S (2014). Biomedical consequences of alcohol use disorders in the HIV-infected host. Curr HIV Res 12: 265–75. [PubMed: 25053365]

Narendran R, Mason NS, Paris J, Himes ML, Douaihy AB, Frankle WG (2014). Decreased prefrontal cortical dopamine transmission in alcoholism. Am J Psychiatry 171: 881–8. [PubMed: 24874293]

Norman MA, Moore DJ, Taylor M, Franklin D Jr., Cysique L, Ake C, Lazarretto D, Vaida F, Heaton RK, Group H (2011). Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version. J Clin Exp Neuropsychol 33: 793–804. [PubMed: 21547817]

Opdebeeck C, Martyr A, Clare L (2016). Cognitive reserve and cognitive function in healthy older people: a meta-analysis. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 23: 40–60. [PubMed: 25929288]

Pandrea I, Happel KI, Amedee AM, Bagby GJ, Nelson S (2010). Alcohol's role in HIV transmission and disease progression. Alcohol Res Health 33: 203–18. [PubMed: 23584062]

Paolillo EW, Gongvatana A, Umlauf A, Letendre SL, Moore DJ (2017). At-Risk Alcohol Use is Associated with Antiretroviral Treatment Nonadherence Among Adults Living with HIV/AIDS. Alcohol Clin Exp Res 41: 1518–1525. [PubMed: 28679147]

Paolillo EW, Inkelis SM, Heaton A, Saloner R, Moore RC, Moore DJ (2019). Age of Last Alcohol Use Disorder Relates to Processing Speed Among Older Adults Living with HIV. Alcohol Alcohol 54: 139–147. [PubMed: 30796775]

Pfefferbaum A, Rosenbloom MJ, Sassoon SA, Kemper CA, Deresinski S, Rohlfing T, Sullivan EV (2012). Regional brain structural dysmorphology in human immunodeficiency virus infection: effects of acquired immune deficiency syndrome, alcoholism, and age. Biol Psychiatry 72: 361–70. [PubMed: 22458948]

Price JC, Thio CL (2010). Liver disease in the HIV-infected individual. Clin Gastroenterol Hepatol 8: 1002–12. [PubMed: 20851211]

Rehm J, Probst C, Shield KD, Shuper PA (2017). Does alcohol use have a causal effect on HIV incidence and disease progression? A review of the literature and a modeling strategy for quantifying the effect. Popul Health Metr 15: 4. [PubMed: 28183309]

Rosenbloom MJ, Sullivan EV, Pfefferbaum A (2010). Focus on the brain: HIV infection and alcoholism: comorbidity effects on brain structure and function. Alcohol Res Health 33: 247–57. [PubMed: 23584066]

Rosenbloom MJ, Sullivan EV, Sassoon SA, O'Reilly A, Fama R, Kemper CA, Deresinski S, Pfefferbaum A (2007). Alcoholism, HIV infection, and their comorbidity: factors affecting self-rated health-related quality of life. J Stud Alcohol Drugs 68: 115–25. [PubMed: 17149525]

Ross JM, Duperrouzel J, Vega M, Gonzalez R (2016). The Neuropsychology of Risky Sexual Behavior. J Int Neuropsychol Soc 22: 586–94. [PubMed: 27173086]

Rothlind JC, Greenfield TM, Bruce AV, Meyerhoff DJ, Flenniken DL, Lindgren JA, Weiner MW (2005). Heavy alcohol consumption in individuals with HIV infection: effects on neuropsychological performance. J Int Neuropsychol Soc 11: 70–83. [PubMed: 15686610]

Saloner R, Marquine MJ, Sundermann EE, Hong S, McCutchan JA, Ellis RJ, Heaton RK, Grant I, Cherner M (2019). COMT Val158Met Polymorphism, Cardiometabolic Risk, and Nadir CD4 Synergistically Increase Risk for Neurocognitive Impairment in Men Living with HIV. J Acquir Immune Defic Syndr.

Sarc L, Lipnik-Stangelj M (2009). Comparison of ethanol and acetaldehyde toxicity in rat astrocytes in primary culture. Arh Hig Rada Toksikol 60: 297–305. [PubMed: 19789159]

Seitz HK, Stickel F (2010). Acetaldehyde as an underestimated risk factor for cancer development: role of genetics in ethanol metabolism. Genes Nutr 5: 121–8. [PubMed: 19847467]

Sharrett-Field L, Butler TR, Reynolds AR, Berry JN, Prendergast MA (2013). Sex differences in neuroadaptation to alcohol and withdrawal neurotoxicity. Pflugers Arch 465: 643–54. [PubMed: 23559099]

Spitzer R, Williams J, Gibbon M, First M (1995). Structured Clinical Interview for DSM-IV. American Psychiatric Press: Washington, DC.

Strömberg P, Svensson S, Hedberg J, Nordling E, Höög J-O (2002). Identification and characterisation of two allelic forms of human alcohol dehydrogenase 2. Cellular and Molecular Life Sciences CMLS 59: 552–559. [PubMed: 11964133]

Sun AY, Sun GY (2001). Ethanol and oxidative mechanisms in the brain. J Biomed Sci 8: 37–43. [PubMed: 11173974]

Sundermann EE, Bishop JR, Rubin LH, Little DM, Meyer VJ, Martin E, Weber K, Cohen M, Maki PM (2015). Genetic predictor of working memory and prefrontal function in women with HIV. J Neurovirol 21: 81–91. [PubMed: 25515329]

Sundermann EE, Heaton RK, Pasipanodya E, Moore RC, Paolillo EW, Rubin LH, Ellis R, Moore DJ (2018). Sex differences in HIV-associated cognitive impairment. Aids 32: 2719–2726. [PubMed: 30407251]

Tedaldi EM, Minniti NL, Fischer T (2015). HIV-associated neurocognitive disorders: the relationship of HIV infection with physical and social comorbidities. Biomed Res Int 2015: 641913. [PubMed: 25815329]

Thomasson HR (1995). Gender differences in alcohol metabolism. Physiological responses to ethanol. Recent Dev Alcohol 12: 163–79. [PubMed: 7624539]

Trantham-Davidson H, Burnett EJ, Gass JT, Lopez MF, Mulholland PJ, Centanni SW, Floresco SB, Chandler LJ (2014). Chronic alcohol disrupts dopamine receptor activity and the cognitive function of the medial prefrontal cortex. J Neurosci 34: 3706–18. [PubMed: 24599469]

Trantham-Davidson H, Centanni SW, Garr SC, New NN, Mulholland PJ, Gass JT, Glover EJ, Floresco SB, Crews FT, Krishnan HR, Pandey SC, Chandler LJ (2017). Binge-Like Alcohol Exposure During Adolescence Disrupts Dopaminergic Neurotransmission in the Adult Prelimbic Cortex. Neuropsychopharmacology 42: 1024–1036. [PubMed: 27620551]

Trantham-Davidson H, Chandler LJ (2015). Alcohol-induced alterations in dopamine modulation of prefrontal activity. Alcohol 49: 773–9. [PubMed: 26558348]

Vance DE (2013). The cognitive consequences of stigma, social withdrawal, and depression in adults aging with HIV. J Psychosoc Nurs Ment Health Serv 51: 18–20. [PubMed: 23521077]

Walker KA, Brown GG (2018). HIV-associated executive dysfunction in the era of modern antiretroviral therapy: A systematic review and meta-analysis. J Clin Exp Neuropsychol 40: 357–376. [PubMed: 28689493]

Wilkinson G, Robertson G (2006). Wide Range Achievement Test-4 (WRAT-4). Psychological Assessment Resources Inc: Lutz, FL.

Wolkowitz OM, Epel ES, Reus VI, Mellon SH (2010). Depression gets old fast: do stress and depression accelerate cell aging? Depress Anxiety 27: 327–38. [PubMed: 20376837]

World Health Organization (1998). Composite Diagnositic International Interview (CIDI, version 2.1). World Health Organization: Geneva, Switzerland.

Yen CH, Yeh YW, Liang CS, Ho PS, Kuo SC, Huang CC, Chen CY, Shih MC, Ma KH, Peng GS, Lu RB, Huang SY (2015). Reduced Dopamine Transporter Availability and Neurocognitive Deficits in Male Patients with Alcohol Dependence. PLoS One 10: e0131017. [PubMed: 26120847]
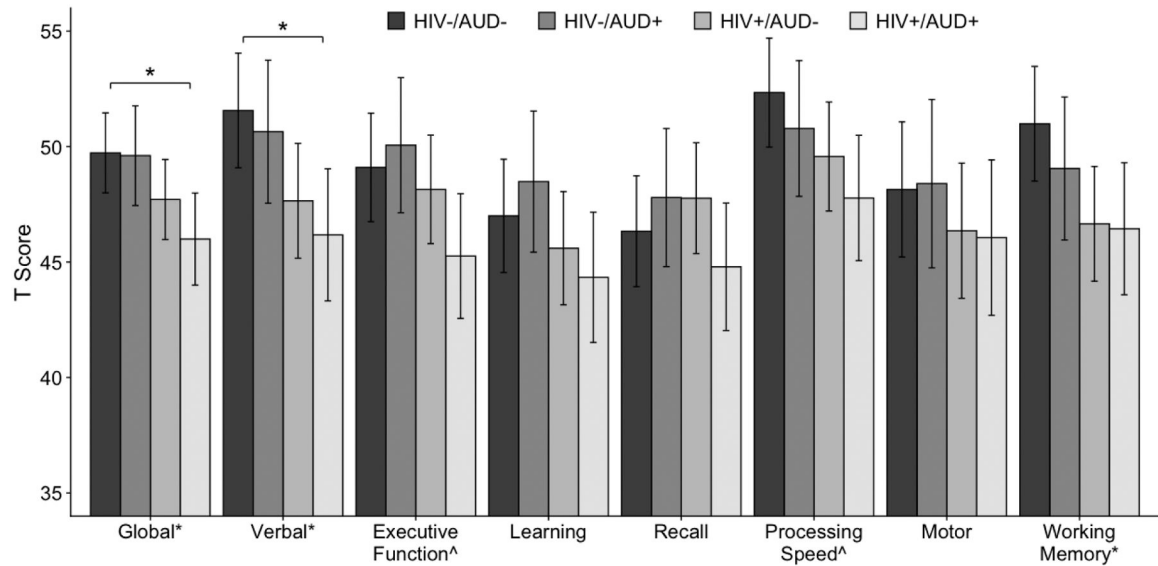
Fig. 1.
Neurocognitive performance by HIV/AUD group. Asterisks next to neurocognitive domains reflect significance for omnibus HIV/AUD group differences. Tukey's HSD pairwise comparison tests indicated significantly lower (worse) global functioning and verbal fluency in HIV+/AUD+ compared to HIV−/AUD−. $*p < 0.05$; $^\wedge p < 0.10$

Fig. 2.
ADH4 (rs1126671) is selectively associated with executive function and working memory in HIV+/AUD+ individuals. Cohen's *d* estimates reflect effect size for A allele vs. GG differences in neurocognitive T scores. **$p < 0.01$; *$p < 0.05$

Table 1.

Distribution of Alcohol Dehydrogenase (ADH) Single-nucleotide Polymorphisms

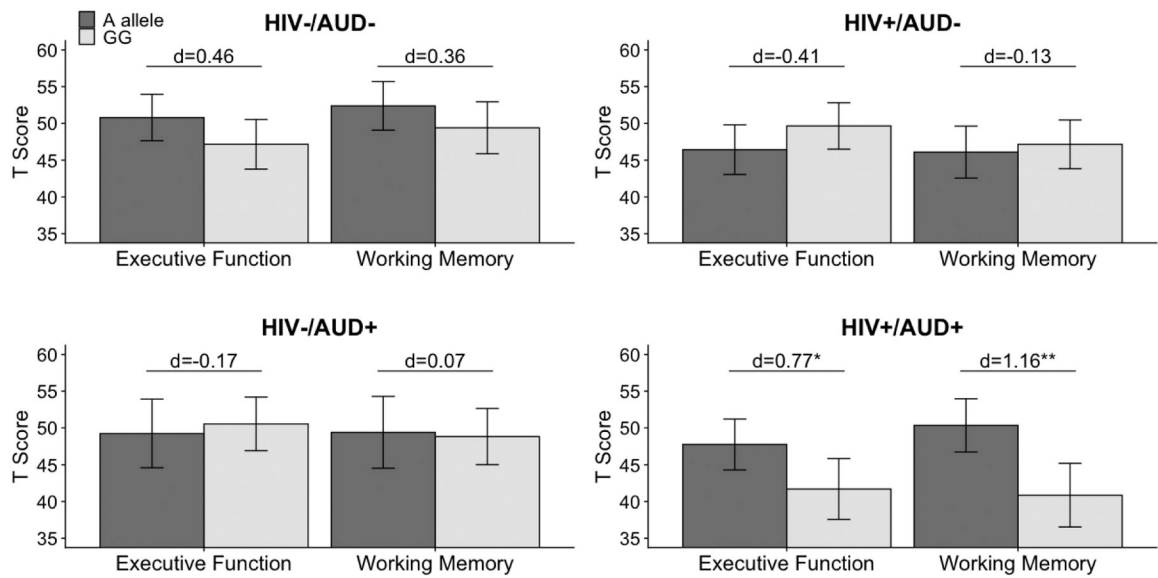| ADH SNP	All variants		Analytic group[a]		HIV−/AUD−	HIV−/AUD+	HIV+/AUD−	HIV+/AUD+
ADH1A	G/G	86 (56.6%)	G/G	86 (56.6%)	26 (57.8%)	15 (53.6%)	23 (51.1%)	22 (64.7%)
rs3819197[b]	A/G	58 (38.2%)	A allele	66 (43.4%)	19 (42.2%)	13 (46.4%)	22 (48.9%)	12 (35.3%)
	A/A	8 (5.3%)						
ADH4	G/G	77 (50.3%)	G/G	77 (50.3%)	21 (46.7%)	18 (62.1%)	24 (53.3%)	14 (41.2%)
rs1126671	A/G	59 (38.6%)	A allele	76 (49.7%)	24 (53.3%)	11 (37.9%)	21 (46.7%)	20 (58.8%)
	A/A	17 (11.1%)						
ADH6	C/C	73 (47.7%)	C/C	73 (47.7%)	20 (44.4%)	17 (58.6%)	22 (48.9%)	14 (41.2%)
rs4699733	G/C	72 (47.1%)	G allele	80 (53.3%)	25 (55.6%)	12 (41.4%)	23 (51.1%)	20 (58.8%)
	G/G	8 (5.2%)						
ADH7	C/C	87 (57.6%)	C/C	87 (57.6%)	26 (59.1%)	16 (57.1%)	27 (60.0%)	18 (52.9%)
rs894369[c]	G/C	52 (34.4%)	G allele	64 (42.4%)	18 (40.9%)	12 (42.9%)	18 (40.0%)	16 (47.1%)
	G/G	12 (7.9%)						
ADH7	G/G	61 (39.9%)	G/G	61 (39.9%)	28 (62.2%)	17 (58.6%)	33 (73.3%)	14 (41.2%)
rs1154470	A/G	74 (48.4%)	A allele	92 (61.1%)	17 (37.8%)	12 (41.4%)	12 (26.7%)	20 (58.8%)
	A/A	18 (11.8%)						

[a]Heterozygotes and homozygous recessive participants were grouped together for statistical analysis.

[b]N = 152

[c]N = 151

Table 2.

Study sample characteristic by HIV/AUD status

	A. HIV–/AUD– (n=45)	B. HIV–/AUD+ (n=29)	C. HIV+/AUD– (n=45)	D. HIV+/AUD+ (n=34)	p	Pair-wise[a]
Demographics						
Age (years)	34.78 (10.17)	36.72 (14.33)	39.22 (11.65)	42.50 (9.44)	0.023	A<D
Education (years)	14.40 (2.75)	13.45 (1.64)	13.13 (2.13)	13.68 (1.89)	0.053	
Race/Ethnicity					0.463	
Black	4 (8.9%)	4 (13.8%)	5 (11.1%)	4 (11.8%)		
Hispanic	14 (31.1%)	8 (27.6%)	8 (17.8%)	4 (11.8%)		
Non-Hispanic White	27 (60.0%)	17 (58.6%)	32 (71.1%)	26 (76.5%)		
WRAT-IV	105.40 (9.61)	101.79 (9.93)	103.73 (11.42)	101.85 (7.44)	0.321	
Psychiatric and medical						
Lifetime non-alcohol substance use disorder	11 (24.4%)	15 (51.7%)	10 (22.2%)	14 (41.2%)	0.023[b]	
Lifetime MDD	9 (20.0%)	8 (27.6%)	21 (46.7%)	19 (55.9%)	0.003	A<C,D
Current MDD	1 (2.2%)	2 (6.9%)	9 (20.0%)	5 (14.7%)	0.034	A<C
BDI-II	1 [0, 3]	3 [0, 8]	7 [3, 12]	7.5 [4, 13]	<0.001	A,B<C,D
Hepatitis C virus	0 (0%)	0 (0%)	3 (6.7%)	6 (17.6%)	0.128	
Alcohol use parameters						
Age of first drink	16.29 (5.22)	15.07 (3.69)	15.76 (4.62)	15.85 (4.32)	0.756	
Days since last drink	4 [1, 28]	4 [2, 31]	14 [4, 61]	7 [2, 274]	0.358	
Lifetime drinking days	506 [164, 1177]	1529 [413, 3349]	462 [195, 1210]	1650 [576, 3853]	<0.001	A,C<B,D
Lifetime drinks	1690 [577, 3922]	7186 [2373, 13543]	1480 [348, 2602]	6734 [3116, 17915]	<0.001	A,C<B,D
Lifetime average drinks per drinking day	3.23 [2, 4.86]	4.29 [3.43, 5.58]	2.51 [1.98, 3.36]	4.40 [3.12, 6.54]	<0.001	C<A<B,D
HIV disease characteristics						
AIDS diagnosis	-	-	19 (42.2%)	20 (58.8%)	0.144	
Estimated years of infection	-	-	4.01 [0.64, 13.24]	8.54 [3.60, 15.57]	0.179	
Nadir CD4	-	-	250 [90, 315]	198 [43, 299]	0.195	
Current CD4	-	-	435 [311, 659]	499 [371, 628]	0.736	
Detectable plasma virus (>50 copies/ml)	-	-	19 (46.3%)	11 (33.3%)	0.257	
Log plasma viral load	-	-	1.70 [1.60, 3.65]	1.70 [1.70, 2.60]	0.762	
On ART	-	-	29 (64.4%)	26 (76.5%)	0.170	

Values are presented as mean (SD), median [IQR], or N; WRAT-IV = Wide-Range Achievement Test-Fourth Edition, reading subtest; MDD = Major Depressive Disorder; HCV=hepatitis C virus; BDI-II = Beck Depression Inventory-II; ART = antiretroviral therapy.

[a] Pair-wise comparisons were examined using Tukey's H.S.D. ($\alpha = 0.05$) for continuous outcomes and Bonferroni-adjustments ($\alpha = 0.05/6 = 0.0083$) for dichotomous outcomes

[b] Pair-wise comparisons for lifetime non-alcohol substance use disorders did not reach statistical significance after Bonferroni-adjustments

Table 3.

Alcohol dehydrogenase (ADH) single-nucleotide polymorphisms moderate the interactive effects of HIV-infection and lifetime alcohol use disorders (AUD) on neurocognition

	2 × 2 × 2 ANOVA			2 × 2 × 2 ANCOVA		
Outcome: Executive Function	*F*	*p*	η_p^2	*F*	*p*	η_p^2
HIV	**5.46**	**0.021**	**0.04**	1.96	0.164	0.01
AUD	0.83	0.363	0.01	0.24	0.624	0.00
ADH4 rs1126671	0.97	0.325	0.01	0.60	0.439	0.00
HIV × AUD	2.63	0.107	0.02	3.08	0.082	0.02
HIV × *ADH4* rs1126671	0.01	0.923	0.00	0.41	0.523	0.00
AUD × *ADH4* rs1126671	0.69	0.408	0.00	0.69	0.408	0.00
HIV × AUD × *ADH4* rs1126671	**7.38**	**0.007**	**0.05**	**5.65**	**0.019**	**0.04**
Age				1.27	0.261	0.01
WRAT				**12.70**	**0.001**	**0.08**
Lifetime Major Depressive Disorder				**10.36**	**0.002**	**0.07**
BDI-II				0.11	0.742	0.00
Lifetime Substance Use Disorder				0.57	0.453	0.00
Outcome: Working Memory	*F*	*p*	η_p^2	*F*	*p*	η_p^2
HIV	**8.09**	**0.005**	**0.05**	**7.81**	**0.006**	**0.05**
AUD	1.04	0.311	0.01	0.29	0.594	0.00
ADH4 rs1126671	**4.79**	**0.030**	**0.03**	**5.64**	**0.019**	**0.04**
HIV × AUD	0.08	0.784	0.00	0.03	0.856	0.00
HIV × *ADH4* rs1126671	0.8	0.373	0.01	1.96	0.164	0.01
AUD × *ADH4* rs1126671	2.21	0.139	0.02	2.43	0.122	0.02
HIV × AUD × *ADH4* rs1126671	**5.58**	**0.020**	**0.04**	**3.94**	**0.049**	**0.03**
Age				3.53	0.062	0.02
WRAT				**6.72**	**0.011**	**0.05**
Lifetime Major Depressive Disorder				**4.56**	**0.034**	**0.03**
BDI-II				1.67	0.199	0.01
Lifetime Substance Use Disorder				1.01	0.317	0.01

Bolded values are significant at $p < 0.05$. WRAT = Wide-Range Achievement reading subtest; BDI-II = Beck Depression Inventory-II