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Effects of smoking and alcohol use on neurocognitive functioning in heavy drinking, HIV-positive men who have sex with men

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Abstract

Cognitive impairment affects approximately half of people living with HIV (PLWH) in the United States, despite improved health outcomes and reduced mortality through widespread use of antiretroviral therapy (ART). Heavy alcohol use and cigarette smoking are potential contributors to neurocognitive impairment in PLWH, yet few studies have examined their influence concurrently. Here we investigated the effects of self-reported alcohol use and smoking on learning, memory, processing speed, verbal fluency, and executive function in 124 HIV-positive men who have sex with men [age (mean ± SD) = 42.8 ± 10.4 years], engaged with medical care. All participants were heavy drinkers. Duration of HIV infection averaged 9.9 ± 7.6 years, and 92.7% were on a stable ART regimen. Participants completed a neuropsychological battery and assessment of past 30-day substance use. Average number of drinks per drinking day (DPDD) was 5.6 ± 3.5, and 33.1% of participants were daily smokers. Rates of neurocognitive impairment were highest in learning (50.8%), executive function (41.9%), and memory (38.0%). Multiple regression models tested DPDD and smoking status as predictors of neurocognitive performance, controlling for age and premorbid intelligence. Smoking was significantly, negatively related to verbal learning (p =

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0.046) and processing speed (p = 0.001). DPDD was a significant predictor of learning (p = 0.047) in a model that accounted for the interaction of DPDD and smoking status. As expected, premorbid intelligence significantly predicted all neurocognitive scores (p's < 0.01), and older age was associated with slower processing speed (p's < 0.01). In conclusion, smoking appears to be associated with neurocognitive functioning deficits in PLWH beyond the effects of heavy drinking, aging, and premorbid intelligence. Smoking cessation interventions have the potential to be an important target for improving functional outcomes in heavy drinking PLWH.

Keywords

smoking; alcohol; human immunodeficiency virus (HIV); cognition; processing speed

Introduction

Antiretroviral therapy (ART) has reduced mortality from human immunodeficiency virus (HIV) infection, yet cognitive impairment continues to affect people living with HIV (PLWH). HIV-associated neurocognitive disorders (HAND) are acquired impairments in cognitive functioning that present along a spectrum of severity and are not attributable to medical or psychiatric comorbidity (Antinori et al., 2007). In the era of ART, the prevalence of HAND is estimated at 44% in those without severe comorbidities (Heaton et al., 2010). Although rates of HIV-associated dementia have declined, milder forms of HAND persist despite viral suppression (Heaton et al., 2011). By definition, the mildest ("asymptomatic") form of HAND entails minimal interference with daily functioning. However, lack of insight into deficits may lead to a self-report bias in prevalence estimates for more severe forms of HAND (Chiao et al., 2013). Recent studies have pointed to comorbidities, extent or timeline of viral suppression, and appropriateness of neuropsychological norms as factors that also may influence HAND prevalence estimates (Crum-Cianflone et al., 2013; Cysique & Brew, 2011; Nightingale et al., 2014).

Heavy alcohol use and smoking frequently co-occur with HIV infection, and may compound HAND. Among PLWH, 65% reported alcohol use in the past year, and 15% endorsed binge drinking in the past 30 days (Centers for Disease Control and Prevention, 2014). HIV infection and alcohol use disorders (AUDs) both are associated with impairment in learning, memory, information processing, and executive functioning (Persidsky et al., 2011). At 41%, the rate of smoking in PLWH is twice that of the general population, and smoking is a major risk factor for cardiovascular disease, non-AIDS cancer, and opportunistic infection (Centers for Disease Control and Prevention, 2014; Lifson et al., 2010). In a previous study, we found that smoking also was significantly associated with impaired learning and memory in PLWH (Bryant, Kahler, Devlin, Monti, & Cohen, 2013). Here we investigated associations of neurocognition with both alcohol use and smoking.

Method

Participants

Participants were 124 MSM living with HIV, recruited from a health center to take part in a clinical trial of a brief intervention for heavy drinking. Baseline, pre-randomization measures are presented here. Inclusion criteria were (1) male; (2) ≥ 18 years old; (3) heavy drinking (≥ 5 drinks) at least once per month, or >14 drinks per week; (4) confirmed diagnosis of HIV; and (5) self-reported sex (insertive or receptive, oral or anal) with a male partner in past 12 months. Participants on ART had to be stable on their current regimen for at least three months. Exclusion criteria were (1) current intravenous drug use; (2) current psychosis, suicidality, or mania, determined with the SCID-NP (First, Spitzer, Gibbon, & Williams, 1995); (3) treatment within the past three months for an HIV-related opportunistic infection; (4) current treatment for alcohol or drug problem; (5) score > 7 on the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) (Sullivan, Sykora, Schneiderman, Naranjo, & Sellers, 1989). Participants were asked to abstain from alcohol for 24 hours before assessment, and zero breath alcohol content was confirmed with breath analysis. Participants provided informed consent in a format approved by the relevant Institutional Review Boards. Table 1 shows participant characteristics.

Measures

Self-report measures—Alcohol and substance use disorders were assessed using the SCID-NP (First et al., 1995). The Timeline Followback Interview (Sobell & Sobell, 1992) was used to assess standard alcoholic drinks consumed (12 oz. beer, 5 oz. wine, or 1.5 oz. 80-proof liquor) and use of drugs in the past 30 days. Participants were designated daily smokers if they reported smoking ≥ 20 days. Depressive symptoms were assessed with the Center for Epidemiological Studies-Depression (CES-D) scale (Radloff, 1977).

Neurocognitive assessment—The battery assessed learning, memory, processing speed, executive function, and verbal fluency. The selected measures (Table 2) are sensitive to deficits associated with HIV and AUDs (Antinori et al., 2007; Cohen et al., 2001; Oscar-Berman et al., 2014). Standardized scores were calculated using published norms (Heaton, Miller, Taylor, & Grant, 2004). Impairment was defined as a score ≥ 1 standard deviation (SD) below the mean of standardized norms (Carey et al., 2004; Heaton et al., 1995).

Statistical analysis

Preliminary analyses examined percentages of participants with impairment in each domain. Next, we examined bivariate correlations between drinking variables and raw cognitive scores. We chose DPDD as the primary alcohol use variable because research has shown that heavy episodic drinking is detrimental to brain function, overall health, and psychosocial functioning (Crews & Nixon, 2009; Holahan, Schutte, Brennan, Holahan, & Moos, 2014). The *a priori* decision to compare daily smokers to a combined group of never, past, and occasional smokers was supported by a preliminary analysis showing no differences in scores among the latter groups and by population-based research (Mons, Schottker, Muller, Kliegel, & Brenner, 2013).

Three sets of multiple linear regression models assessed the effects of selected predictors on cognitive functioning. We used raw scores because adjustments for demographic factors (i.e., age, education, race) were inconsistent across test norms. The preliminary analysis included age, WTAR, education, race, drug use (current/past cannabis dependence, any drug use, or any non-cannabis drug use), and CES-D score as covariates. The final models were chosen through a backward selection procedure, in which we removed non-significant covariates one step at a time. Education, race, drug use, and CES-D were non-significant and thus were not retained in subsequent models. The first set of regression models tested associations of DPDD and smoking status with cognitive scores, controlling for age. In the second set of regression models, we tested these associations controlling for age and WTAR. The third set of regression models included an interaction term for smoking and DPDD. Alpha level was set to .05 for statistical significance.

Results

Rates of cognitive impairment

Rates of impairment in learning (50.8%), executive function (41.9%), and memory (38.0%) exceeded the 16% expected on the basis of the normal distribution (Table 3).

Contributions of smoking status and alcohol use to cognitive performance

Drinks per drinking day (DPDD) showed consistent associations with neurocognitive scores in bivariate correlations (Table 4). The first set of regression models (Table 5), controlling for age, showed a significant, negative association of current smoking with learning, memory, and processing speed. Age was a significant predictor of processing speed. Premorbid functioning was a significant predictor of all domains across models.

In the second set of regression models, controlling for age and premorbid intelligence, smoking status was a significant predictor of learning and processing speed. Age remained a significant predictor of processing speed.

In the third set of models, which included the interaction of DPDD and smoking status, the interaction term was a significant predictor of learning, as were DPDD and smoking status individually. The direction for the interaction effect was opposite to individual effects for DPDD and smoking status. Post hoc follow-up analysis showed that the slope for DPDD on learning was negative for non-daily smokers ($B = -0.06$, $p = 0.610$) but positive for daily smokers ($B = 0.22$, $p = 0.114$).

Finally, the possibility that neurocognitive deficits associated with smoking might be related to lifetime substance exposure was explored in a post hoc chi-square test on binary (yes/no) variables for current smoking and lifetime substance use disorder. Current smokers were significantly more likely to report lifetime substance use disorders than non-smokers, $\chi^2(1) = 9.59$, $p = 0.002$.

Discussion

In this study, we found elevated rates of impairment in learning, executive function, and memory in heavy-drinking, HIV-positive MSM, consistent with previous studies on HIV infection and alcohol use (Persidsky et al., 2011). The main findings further our understanding of neurocognition in PLWH. First, daily smoking was significantly associated with decrements in verbal learning and processing speed, and these associations persisted after controlling for premorbid intelligence, age, and alcohol use. This finding replicates and extends key aspects of our earlier study showing that smoking predicted poorer learning, memory, and global cognition in an independent sample of PLWH (Bryant et al., 2013). Regarding clinical and functional implications, previous research identified the measure of processing speed associated with smoking status, the Digit Symbol test, as a strong independent predictor of quality of life in PLWH (Tozzi et al., 2003). Second, premorbid intelligence significantly predicted performance in all domains, and age significantly predicted processing speed. These results underscore the importance of using demographically appropriate norms and comparing an individual's current functioning to his or her own baseline where possible. Third, DPDD showed correlations with memory, processing speed, and verbal fluency, but associations were not significant in adjusted models. A significant negative effect of DPDD on learning emerged when including the interaction of DPDD and smoking. However, the interaction effect, in which DPDD had a positive slope on learning for daily smokers and negative slope for non-daily smokers, is difficult to interpret and underscores the non-causal nature of findings in this observational study.

Generalizability is limited by the all-male sample and high average educational attainment. An important future direction is to compare HIV-positive and HIV-negative groups of MSM to quantify the direct influence of HIV infection on neurocognition after accounting for methodological, demographic, and behavioral factors.

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Table 1

Sociodemographic and clinical characteristics ($N = 124$).

	Mean (SD) or %
Age (years)	42.8 (10.4)
Race[a]	
White (%)	73.4
African-American (%)	32.0
Overweight (%)	62.1
Education	
Less than high school (%)	1.6
High school (%)	10.5
Some college or vocational training (%)	41.1
College graduate or beyond (%)	46.8
Unemployed (%)	36.3
Duration of HIV infection (years)	9.9 (7.6)
CD4 count nadir ($n = 115$)	343.5 (209.5)
Hepatitis C virus coinfection (%)	7.3
Undetectable viral load (%)	91.1
Currently on ART[b] (%)	92.7
Current use of ART by drug class[c]	
Nucleoside reverse transcriptase inhibitor (%)	45.1
Nonnucleoside reverse transcriptase inhibitor (%)	6.5
Protease inhibitor (%)	50.8
HIV integrase strand transfer inhibitor (%)	8.9
CCR5 co-receptor antagonist (%)	1.6
Multi-class combination drug (%)	41.9
Smoking status	
Never smoker (%)	15.0
Past smoker (%)	31.5
Occasional smoker (%)	20.2
Current daily smoker (%)	33.1
Alcohol dependence diagnosis	
Never (%)	29.8
Past (%)	32.3
Current (%)	37.9
Number of drinking days[b]	16.9 (8.5)
Average drinks per drinking day[b]	5.6 (3.5)
Total number of drinks[b]	93.3 (91.0)
Number of heavy drinking days[b]	7.4 (6.9)
Percentages reporting any use of other drugs[b]	

	Mean (SD) or %
Marijuana (%)	44.4
Methamphetamine (%)	8.9
Cocaine (%)	23.4
Poppers/inhalants (%)	18.5
None (%)	34.7
Number of substance use days[b]	
Marijuana	6.3 (10.4)
Methamphetamine	0.2 (0.9)
Cocaine	1.0 (3.3)
Poppers/inhalants	0.9 (2.4)
Current cannabis dependence (%)	6.5
Current non-cannabis substance dependence (%)	8.1
Current depression diagnosis (n = 119) (%)	9.7
Center for Epidemiological Studies Depression (CES-D) score	6.2 (12.2)

[a] Three participants endorsed more than one racial category.

[b] Assessed with Timeline Followback Interview covering past 30 days.

[c] Sum of percentages exceeds 100% because participants could report taking multiples classes of ART.

Table 2

Neurocognitive battery

Domain	Measure
Premorbid intelligence	Wechsler Test of Adult Reading (WTAR) score (Wechsler, 2001)
Learning	Hopkins Verbal Learning Test-Revised (HVLT) total recall (Benedict, Schretlen, Groninger, & Brandt, 1998)
Memory	HVLT delayed recall
Processing speed	**a)** Digit Symbol score from Wechsler Adult Intelligence Scale—3rd edition (Wechsler, 1997) **b)** Trails A test time (Reitan, 1992)
Executive function	Trails B test time (Reitan, 1992)
Verbal fluency	Controlled Oral Word Association Test (COWAT) total score (Benton, Hamsher, & Sivan, 1994)

Note: Higher score indicates better performance for all tests except Trails A and Trails B, for which higher time score indicates worse (i.e., slower) performance.

Table 3

Standardized neurocognitive test scores (*N*=124).

Test and associated domain	Mean (SD)	% impaired
WTAR (premorbid intelligence)	107.3 (15.0)	N/A
HVLT total recall (learning)	39.3 (11.0)	50.8
HVLT delayed recall (memory)[a]	42.4 (12.3)	38.0
Digit Symbol (processing speed)	48.0 (9.4)	16.1
Trails A time (processing speed)	49.4 (10.2)	15.3
Trails B time (executive function)	41. 5 (17.5)	41.9
COWAT (verbal fluency)[a]	52.1 (11.2)	12.9

Note: Impairment was defined as a score ≥ 1 SD below the mean for published norms.

Abbreviations: COWAT = Controlled Oral Word Association Test; HVLT = Hopkins Verbal Learning Test; WTAR = Wechsler Test of Adult Reading.

[a] n = 123

Table 4

Pearson correlations between neurocognitive raw scores and drinking behavior.

	DPDD	Total number of drinks	Number of heavy drinking days
Learning (HVLT total recall)	−0.16	−0.09	−0.11
Memory (HVLT delayed recall)	−0.24**	−0.17	−0.12
Processing speed (Digit Symbol)	−0.21*	−0.21*	−0.12
Processing speed (Trails A)	0.17	0.13	0.04
Executive function (Trails B)	0.00	0.02	0.02
Verbal fluency (COWAT)	−0.21*	−0.17	−0.17

Note: Higher scores correspond to better performance for HVLT, Digit Symbol, and COWAT measures. Lower scores indicate better performance for Trails A and Trails B.

Abbreviations: COWAT = Controlled Oral Word Association Test; DPDD = drinks per drinking day; HVLT = Hopkins Verbal Learning Test.

** significant at $p < 0.01$;

* significant at $p < 0.05$.

Table 5

Multivariate regression models predicting neurocognitive performance.

Domain and measure	Predictors	Model 1[a]		Model 2[b]		Model 3[c]	
		Estimate	p-value	Estimate	p-value	Estimate	p-value
Premorbid intelligence (WTAR)	Age	0.05	0.542	-	-	-	-
	DPDD	−0.65	0.011	-	-	-	-
	Daily Smoker	−4.06	0.035	-	-	-	-
Learning (HVLT total recall)	WTAR	-	-	0.18	< 0.001	4.86	< 0.001
	Age	−0.05	0.164	−0.06	0.081	−2.18	0.031
	DPDD	−0.11	0.365	0.01	0.934	−2.01	0.047
	Daily Smoker	−2.48	0.007	−1.73	0.046	−3.19	0.002
	DPDD × Daily Smoker	-	-	-	-	2.47	0.015
Memory (HVLT delayed recall)	WTAR	-	-	0.09	< 0.001	4.42	< 0.001
	Age	−0.03	0.176	−0.03	0.076	−1.77	0.080
	DPDD	−0.10	0.087	−0.04	0.443	−0.47	0.640
	Daily Smoker	−1.19	0.008	−0.81	0.056	−1.09	0.278
	DPDD × Daily Smoker	-	-	-	-	0.05	0.959
Processing speed (Digit Symbol)	WTAR	-	-	0.56	< 0.001	4.33	< 0.001
	Age	−0.34	0.006	−0.37	0.002	−3.11	0.002
	DPDD	−0.46	0.223	−0.10	0.783	0.17	0.867
	Daily Smoker	−11.65	< 0.001	−9.38	0.001	−1.56	0.122
	DPDD × Daily Smoker	-	-	-	-	−0.39	0.701
Processing speed (Trails A)	WTAR	-	-	−0.34	< 0.001	−3.22	0.002
	Age	0.30	0.002	0.32	0.001	3.41	0.001
	DPDD	0.44	0.140	0.22	0.451	0.30	0.765
	Daily Smoker	3.91	0.082	2.55	0.245	0.51	0.609
	DPDD × Daily Smoker	-	-	-	-	0.14	0.888
Executive function (Trails B)	WTAR	-	-	−4.51	< 0.001	−5.51	< 0.001
	Age	0.58	0.470	0.81	0.265	1.07	0.286
	DPDD	−1.35	0.591	−4.28	0.065	−1.18	0.242
	Daily Smoker	31.60	0.096	13.28	0.441	0.27	0.788
	DPDD × Daily Smoker	-	-	-	-	0.18	0.860
Verbal fluency (COWAT)	WTAR	-	-	0.50	< 0.001	3.78	< 0.001
	Age	−0.13	0.299	−0.16	0.171	−1.40	0.165
	DPDD	−0.74	0.054	−0.41	0.270	−0.84	0.403
	Daily Smoker	−2.65	0.357	−0.51	0.854	−0.33	0.743

Domain and measure	Predictors	Model 1[a]		Model 2[b]		Model 3[c]	
		Estimate	p-value	Estimate	p-value	Estimate	p-value
	DPDD × Daily Smoker	-	-	-	-	0.27	0.786

Note: Higher scores indicate better performance for WTAR, HVLT, Digit Symbol, and COWAT measures. Lower scores indicate better performance for Trails A and Trails B.

Abbreviations: DPDD = drinks per drinking day; COWAT = Controlled Oral Word Association Test; HVLT = Hopkins Verbal Learning Test-Revised; WTAR = Wechsler Test of Adult Reading.

[a]Model 1: Regression analysis including all covariates in the table except WTAR

[b]Model 2: Regression analysis including all covariates in the table

[c]Model 3: Regression analysis including all covariates and the interaction of daily smoking and DPDD