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The effects of cigarette smoking on learning and memory performance among people living with HIV/AIDS

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Abstract

The purpose of the present study was to examine the effects of smoking (past and current) on multiple domains of cognitive functioning in a sample of people living with HIV/AIDS (PLWHA). We hypothesized that among PLWHA, current smokers would demonstrate poorer cognitive functioning when compared to non-smokers, specifically in the cognitive domains of auditory-verbal (AV) learning and memory, visuospatial memory, overall cognitive efficiency, executive skills, processing speed and working memory. Results suggest that in patients being treated for HIV infection, current smoking is negatively associated with learning, memory and global cognitive functioning. There also was some evidence that cognitive deficits in learning associated with smoking were more pronounced among men compared to women. However, the cause of these effects is not at all clear. In multivariate models, the differences associated with smoking were non-significant when adjusting for education and hepatitis C (HCV) infection. Therefore, smoking may simply reflect a general tendency to more widespread deficits and comorbidities rather than directly impacting cognitive function. Future studies should attempt to examine a priori cognitive factors which contribute to smoking debut and other associated risk factors in order to understand why smoking may be a marker for other risk factors and may ultimately influence neurocognitive functioning critical to daily activities and adherence.

Introduction

Rates of cigarette smoking are high among people living with HIV/AIDS (PLWHA), at an estimated range between 40–70% (Durazzo et al., 2007; Crothers et al., 2005; Burns et al., 1996; Page-Shafer et al., 1996; Galai et al., 1997; Niaura et al., 2000; Turner et al., 2001; Diaz et al., 2003). This greatly eclipses the rate of current daily smoking in the general US population, which is an estimated 20.6% (CDC, MMWR. 2010). Current cigarette smoking among PLWHA has been associated with a number of health problems, including increased respiratory symptoms, COPD, bacterial pneumonia, and decreased quality of life, even after adjusting for other factors such as demographics, HIV disease severity, and substance use (Crothers, 2005). The extent to which smoking is associated with neurocognitive impairment among PLWHA has been less studied.

The presence of a detectable HIV viral load has been associated with neurocognitive impairment, particularly in specific measures, within the domains of: attention/working

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memory/executive function, processing speed, memory, verbal fluency and overall cognitive functioning (Devlin et al., 2012). Evidence suggests that HIV infection may lead to neurodegenerative effects independent of comorbid conditions due to immune response and chronic neuro-inflammation (Palacio, 2011; Ballester et al., 2011). These neurocognitive deficits, ranging from mild impairment to dementia, have been collectively labeled HIV-Associated Neurological Disorders (HAND; Gannon et al., 2011). Prevalence rates of HAND often exceed 50 percent among PLWHA in the US, with many individuals demonstrating mild or asymptomatic impairments (Heaton et al., 2011; Valcour et al., 2011). Neurocognitive functioning is critical to many domains of health and everyday functioning, particularly in PLWHA. For example, neurocognitive impairment has been associated with poor adherence to antiretroviral therapy (ART) (Schouten, 2011), higher rates of cardiovascular problems (Wright et al., 2010) and lower quality of life (Crothers, 2005). PLWHA often have comorbid substance abuse disorders which may contribute to neurocognitive dysfunction in their own right; however, the relationship between substance abuse and HAND has not yet been fully elucidated (Nath, 2010). Given that tobacco, in the form of cigarette smoking, is one of the most commonly used drugs among PLWHA, it is therefore important to examine how smoking contributes to neuropsychological deficits in PLWHA.

In the general population there is evidence of deleterious long-term effects of smoking on cognition. A review examining the effects of chronic cigarette smoking on neurocognition found that people who identified as being either current or past smokers performed worse than non-smokers in global cognitive functioning and cognitive flexibility and had higher risk of global cognitive impairment, (Durazzo et al., 2010, p. 45–46). Among middle aged adults who are current smokers, longitudinal research suggests a steeper decline with age in measures of reasoning and auditory-verbal memory, as compared to non-smokers (Durazzo et al., 2010; Sabia et al., 2008; Richards et al., 2003).

There have been multiple cited mechanisms for explaining the relationship between cigarette smoking and neurocognitive impairment. These include the direct cytotoxicity to neuronal and glial cells of compounds found in cigarette smoke (Durazzo, Meyerhoff & Nixon, 2010; Fowles, Bates & Noiton, 2000), as well as through the indirect effects of smoking on obesity and insulin resistance, which are directly linked with higher rates of neurocognitive impairment (Chiolero et al., 2008).

To our knowledge only two studies have examined the effects of cigarette smoking on neurocognitive functioning among PLWHA, and these have yielded contradictory findings. One study of 44 HIV-positive heavy drinkers (Durazzo et al. 2007) found that those who smoked performed significantly worse than those who did not smoke in the cognitive domains of auditory-verbal (AV) learning, AV memory and cognitive efficiency. However, this study only included smokers who were also heavy drinkers and did not account for previous smoking history or the quantity of cigarettes smoked per day. The second study (Wojna et al., 2007) examined the effects of smoking on neurocognitive impairment among 56 HIV-positive and HIV-negative females. There were no significant differences in cognitive impairment between HIV-positive and HIV-negative smokers. However, when the analyses were restricted to HIV-positive females, those with a history of smoking performed significantly better on the frontal/executive domain than those without a history of smoking. No large studies have examined the contribution of smoking to neurocognitive impairment in HIV-positive men and women.

Study Aims

The purpose of the present study was to examine the effects of smoking (past and current) on multiple domains of cognitive functioning in a sample of PLWHA. We hypothesized that

among PLWHA, current smokers would demonstrate poorer cognitive functioning when compared to non-smokers, specifically in the cognitive domains of auditory-verbal (AV) learning and memory, visuospatial memory, overall cognitive efficiency, executive skills, processing speed and working memory. We hypothesized that these differences would persist when controlling for demographic factors, previous history of alcohol or drug use disorders, current alcohol use, HCV infection, and being on ART.

Method

One hundred twenty-five HIV-infected participants were recruited, and 115 completed neurocognitive assessments. Participants were recruited from The Miriam Hospital Immunology Center from an NIH-funded study on HIV associated brain dysfunction. Additional demographic characteristics of the sample are summarized in Devlin (2012). The study was approved by the institutional review boards at The Miriam Hospital and Brown University, and informed consent was obtained from each participant before enrollment. All participants underwent a neurological examination and thorough medical history assessment. HIV infection was documented by enzyme-linked immunosorbent assay (ELISA) and confirmed by Western blot. Participants were excluded for history of (1) head injury with loss of consciousness longer than 10 minutes; (2) history of neurological conditions including dementia, seizure disorder, stroke, and opportunistic infection of the brain; (3) severe psychiatric illness that might impact brain function, (e.g.) schizophrenia; and (4) current (6-month) substance dependence or positive urine toxicology screen for cocaine, opiates, or illicit stimulants or sedatives.

Mean duration of HIV infection was 12.6 years, and the majority (82.6%) of the sample was on stable combination ART. Forty-two (36.5%) had active HCV infection, see Devlin (2012) for definition of active HCV infection. Smoking status was measured through self-report, with 74 (64.3%) participants reporting current smoking. Fifteen (13.0%) reported being past but not current smokers, and 26 (22.6%) reported never having smoked. Among current smokers, the average number of cigarettes smoked per day was 13. Current drinking, current drug use and lifetime alcohol use disorder were all assessed using individual self-report items. Depressive symptoms were assessed using the Center for Epidemiologic Studies Depression Scale (CES-D; Radloff, 1977).

Neurocognitive Assessments

The following domains of neurocognitive functioning were assessed: speed of information processing, attention/working memory/executive functioning, learning, memory, verbal fluency, and psychomotor speed. The battery consisted of the following tests, which were chosen for their sensitivity to HAND: Hopkins Verbal Learning Test – Revised (HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998; Brandt & Benedict, 1991); Brief Visuospatial Memory Test – Revised (BVMT-R; Benedict, 1997); Controlled Oral Word Association Test (COWAT–FAS; Benton, Hamsher, & Sivan, 1994); category fluency (animals); Stroop Color and Word Test (Golden, 1978); Trail Making Test, Parts A and B (Reitan, 1992); Grooved Pegboard Test (Kløve, 1963); and the Digit Symbol– Coding, Symbol Search, and Letter-Number Sequencing tests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Wechsler, 1997). The present tests and domains are similar to those used in the Global Deficit Score (GDS), which has shown high validity in detecting HIV-associated neurocognitive impairment (Carey et al., 2004; Heaton et al., 1995). Demographically corrected t scores were calculated using established norms (Benedict et al., 1998; Benedict et al., 1996; Heaton, Miller, Taylor, & Grant, 2004). Domain composite scores were calculated by averaging the t scores of all tests in the domain. Overall composite scores were calculated by averaging the t scores of all tests in the battery.

Statistical Analysis

Differences among never, past, and current smokers in demographics, depressive symptoms, history of alcohol abuse, current drinking status, HCV infection, CD4 count and viral load were assessed using analysis of variance or Pearson's $\chi 2$ (see Table 1). To test for differences in cognitive function between the three smoking groups, regression models with orthogonal contrast coding were conducted. The first contrast compared current vs. non-current smokers (i.e., both never and past smokers). The second contrast compared never smokers vs. past smokers. Given that no significant differences in neurocognitive variables were found for the never vs. past contrast, these groups were collapsed for all analyses of cognitive outcomes, leaving us with a dummy-coded contrast of 0 = non-current smoker and 1 = current smoker. We first ran unadjusted regression models to test which domains showed significant differences between current smokers and current non-smokers. For those domains where a significant effect was present, we then ran hierarchical models entering additional covariates that might confound the association between smoking and cognitive function. The first step included smoking status as a predictor of the domain. The second step added potentially relevant demographic variables, including age, and education. The third step added other clinical characteristics that might be associated with smoking and with cognitive function including history of drug use and substance use disorder, current alcohol use, and HCV status. HCV status has previously been shown to be a robust predictor of neurocognitive functioning in this sample (Devlin et al., 2011). In addition, because a prior study showed a potential beneficial effect of smoking in HIV-infected women and because Crystal et al. (2012) found that HCV among women does not affect neurocognitive functioning, we repeated these analyses by gender.

Results

Background Characteristics

As shown in Table 1, current smokers were the youngest group with an average age of 44.09, about 4 years younger than never smokers. Years of education were significantly different across groups with never smokers averaging 2 more years of education than current smokers. Smoking groups differed significantly in level of depressive symptoms, which were highest among current smokers. Rates of current drinking differed significantly by smoking status and were highest among never smokers at around 81 percent. Current HCV rates differed significantly by smoking status and were highest among current smokers at around 45 percent.

Neurocognitive Variables

Results of unadjusted regression analyses predicting neurocognitive domains are shown in Table 2. Significant differences by smoking status were found for learning, memory and global functioning, with current smokers performing worse than non-smokers. Hierarchical regression analyses were performed next in order to examine whether these differences remained when controlling for other relevant characteristics that might confound the association between smoking and cognitive functions. Among the demographic variables, age, gender, and race where not associated with neurocognitive function, whereas education was. Among the clinical characteristics, drinking and drug use variables were not significantly associated with neurocognitive function, whereas HCV status was. Additionally, there were no significant differences in performance associated with number of cigarettes smoked per day and duration (number of years smoked). Given our modest sample size and the desire for a parsimonious model, we therefore ran the following steps in the model: Step 1 – smoking contrast; Step 2 smoking contrast and education; Step 3 – smoking contrast, education, and HCV. Results are presented in Table 3. Smoking contrast

was significantly associated with learning, memory and global scores, with current smokers scoring lower on all domains. However, this effect became non-significant once education was entered into the model for each domain. Education was directly associated with learning, memory and global scores for both steps 2 and 3. HCV was significantly associated with the memory domain, with active HCV infection associated with poorer neurocognitive performance.

Finally, we repeated this hierarchical analysis by gender. The results are presented in Table 5. HCV was a significant predictor of learning and memory impairment among men even when education and smoking were included in the model. Smoking was a significant predictor of learning impairment among men, although this effect became non-significant after adding education and HCV to the model. Among women, neither smoking, nor HCV predicted neurocognitive performance on any of the domains.

Discussion

Results suggest that in patients being treated for HIV infection, current smoking is negatively associated with learning, memory and global cognitive functioning. There also was some evidence that cognitive deficits in learning associated with smoking were more pronounced among men compared to women. However, the cause of these effects is not at all clear. In multivariate models, the differences associated with smoking were nonsignificant when adjusting for education and HCV infection. Therefore, smoking may simply reflect a general tendency to more widespread deficits and comorbidities rather than directly impacting cognitive function. Indeed, based on a large study of healthy individuals, Wagner et al., (2010) suggested that there may be a pre-existing cognitive endophenotype, which predisposes individuals to smoke, and contributes to lower neurocognitive performance. In that study, smokers showed small but specific neurocognitive deficits within the domains of visual attention and cognitive impulsivity. However, duration or number of cigarettes smoked was not correlated with differences in neurocognitive performance, which suggest that there may be some underlying subgroup difference among smokers. Likewise, in the present study, even though a unique role of smoking in neurocognitive function was not demonstrated, there are potential clinical implications for study results.

Compared to non-smokers, smokers showed a variety of characteristics that might complicate treatment of these patients. Not only does smoking itself contribute directly to adverse health outcomes, HIV patients who smoke showed especially low levels of education, elevated depressive symptoms, and high rates of HCV infection. Results of other studies suggest that smoking may be an independent risk factor for sexual risk behaviors and STI diagnoses (Berg et al., 2012) and among those who have current HCV, smoking is associated with higher levels of viremia (Operskalski, 2008). Taken together, these studies suggest that smoking may serve as marker for a variety of comorbid conditions that can complicate treatment. When combined with worse cognitive function and lower levels of education, these patients may be at especially high risk of non-adherence to medication and difficulty quitting smoking. Depressive symptoms consistently predict both poor smoking cessation outcomes (Leventhal et al., 2012; Kahler et al., 2004). These results suggest that efforts to promote smoking cessation in HIV-infected patients may be particularly challenging. Indeed, smoking cessation interventions in patients with HIV have had low success rates (Humfleet et al., 2009 ; Stanton et al., 2009; Gritz et al., 2004). Interventions for HIV-infected smokers may need to address both depressive symptoms and cognitive deficits to be maximally effective. Likewise, elevated depressive symptoms and neurocognitive deficits are both associated with poor HAART adherence (Wagner et al.,

2011), and future studies should examine the extent to which smoking predicts poor medication adherence.

Approximately 50% of HIV positive individuals will be over 50 within the next 3–5 years (Sankar et al., 2011; Effros et al., 2008). The data analyzed were cross-sectional. Therefore, it is not possible to discern whether smoking is associated with more steep declines in cognitive functioning with aging. Future studies should examine the longitudinal effects of smoking on neurocognition, tracking individuals into their 50s and 60s. Aging and HIV has become an important issue, especially considering that over half of PLWHA are projected to be over 50, by 2015 (Stoff et al., 2004; Wendelken & Valcour, 2012). Among the general population, in two separate samples of older adults (55+), current smoking, but not past smoking, increased the risk of dementia. (Otto et al., 1997; Reitz et al., 2007; Lee et al., 2010). Therefore, effects of smoking on neurocognitive function may become more pronounced with aging and efforts should be made to promote smoking cessation before those deficits become manifest.

As noted in a prior study with this sample (Devlin et al., 2011), HCV was a robust predictor of cognitive function. Interestingly gender analyses indicated that Hepatitis C was a significantly associated with learning and memory scores in males, whereas in females, HCV did not significantly affect neurocognitive scores in any of the domains. Frequency of HCV did not significantly differ by gender. It is often difficult to parse out the effects of particular variable such as smoking and HCV because these variables tend to accompany other comorbid factors such as history drug and alcohol abuse, HIV, psychiatric disorders, and impaired liver functioning (Senzolo, 2011). However, HCV has previously been associated with poorer visuospatial memory performance in a sample without dual infection, after controlling for age and education (Quarantini, 2009). The results of this study were consistent with findings suggested of Crystal et al., (2012), indicating that HCV may affect neurocognitive functioning differently among women as compared to men. The findings of this study also suggest that smoking may be an independent risk factor for other health outcomes.

Limitations

The main limitations were that the study was cross-sectional, that sample sizes for comparing never and past smokers were small, and that the overlap between HCV and smoking made it impossible to test with adequate power whether smoking has an effect in the absence of HCV. There was also a large overlap between smoking and education level, which made it difficult to parse out the main effect of smoking over and above the influence of education.

Conclusions

To conclude, smoking among people living with HIV is associated with moderate decrements in learning and memory and global cognitive performance. However, much of the influence of smoking on neurocognitive impairment may be better understood by viewing smoking a marker for other health and demographic risks associated with lower neurocognitive performance, such as lower education and increased rates of Hepatitis C. Future studies should attempt to examine a priori cognitive factors which contribute to smoking debut and other associated risk factors in order to understand why smoking may be a marker for other risk factors. Clinical care for smokers living with HIV needs to consider that these patients have high rates of other risk factors for poor health outcomes, including worse neurocognitive functioning which can influence adherence to ART.

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Table 1

Demographic and Clinical Characteristics by Smoking Status

	Total (n = 115)	Never Smoked (n=26)	Ever smoked non-current (n=15)	Current Smoker (n=74)	*P*
Variable	**% or Mean (SD)**	**% or Mean (SD)**	**% or Mean (SD)**	**% or Mean (SD)**	
Demographics					
% Male	62.6	19(73.1)	11(73.3)	42(56.8)	*ns*
Age(Years)	45.36(9.48)	48.23(9.89)	46.6(7.37)	44.09(9.57)	*ns*
Race					
Caucasian	53.9	53.8	53.3	54.1	ns
African American	26.1	23.1	26.7	27	ns
Education (years)	12.43(2.13)	13.88(2.23)	12.4(1.92)	11.93(1.91)	B
Lifetime Psychiatric					
Diagnoses/Comorbidities					
CESD	21.5(12.68)	17.08(13.37)	17.33(12.26)	23.88(12.04)	B
Current Drinker (n = 60)	52.6	80.8	13.3	50.7	A,B,C
Alcohol Abuse (n = 39)	33.9	11.5	46.7	39.7	*ns*
HCV Current (n = 42)	36.5	15.4	33.3	44.6	B
Current Drug Use(n = 31)	27	11.5	13.33	35.13	*ns*
HIV Markers					
CD4 Current	461.19(245.4)	499.6(230.99)	483.53(282.21)	443.45(243.87)	ns
CD4 Nadir	180.84(154.1)	160.46(136.62)	119.87(111.48)	200.36(164.36)	ns

Note. Results are presented as mean (SD) or frequency (percentage) unless otherwise noted. . A = never vs. former, p<.01; B = never vs. current, p<.01; C = former vs. current, p<.01

Table 2

Neurocognitive Performance by Current Smoking Status

	B	SE	Beta	P
Processing Speed	−1.130	1.312	−0.081	0.391
Attention/Exec	−1.574	1.509	−0.098	0.299
Learning	−4.927	1.996	−0.226	**0.015***
Memory	−5.782	2.577	−0.207	**0.027***
Verbal	−1.206	1.451	−0.078	0.408
Motor	−2.507	2.128	−0.110	0.241
Global	−2.662	1.158	−0.211	**0.023***

Note.

*P<.05.

Each domain was assessed using the following tests **Processing Speed** (Digit Symbol-Coding, Symbol Search, Trail Making Test Part A) **Attention/WM/executive** (Letter Number Sequencing, Trail Making Test Part B, Stroop Interference) **Learning** (HVLT total recall, BVMT total recall) **Memory** (HVLT delayed recall, BVMT delayed recall) **Verbal** (FAS letter fluency, Category fluency), **Motor** (GP dominant hand, GP non-dominant hand)

Table 3

Hierarchical Analyses of Smoking, Education, and HCV as Predictors of Learning, Memory and Global Cognitive Function

Learn	**Step 1**	**Step 2**	**Step 3**
Smoking Contrast	**−0.226***	−0.071	−0.051
Education		**0.487***	**0.444***
HCV			−0.149
Mem	Step 1	Step 2	Step 3
Smoking Contrast	**−0.207***	−0.051	−0.026
Education		**0.49***	**0.438***
HCV			**−0.182***
Glob	Step 1	Step 2	Step 3
Smoking Contrast	**−0.211***	−0.079	−0.062
Education		**0.416***	**0.382***
HCV			−0.122

Note.

*p<0.05

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Table 4

Hierarchical Analyses of Smoking, Education, and HCV as Predictors of Learning, Memory and Global Cognitive Function within Gender

Men				**Women**			
Learn	Step 1	Step 2	Step 3	Learn	Step 1	Step 2	Step 3
Smoking Contrast	**−0.273***	−0.104	−0.072	Smoking Contrast	−0.053	−0.016	−0.016
Education		**0.435***	**0.357***	Education		**0.467***	**0.467***
HCV			**-0.263***	HCV			−0.001
Memory	Step 1	Step 2	Step 3	Memory	Step 1	Step 2	Step 3
Smoking Contrast	−0.181	−0.001	0.031	Smoking Contrast	−0.168	−0.13	−0.119
Education		**0.463***	**0.385***	Education		**0.478***	**0.459***
HCV			**−0.263***	HCV			−0.072
Global	Step 1	Step 2	Step 3	Global	Step 1	Step 2	Step 3
Smoking Contrast	−0.226	−0.085	−0.07	Smoking Contrast	−0.102	−0.068	−0.048
Education		**0.362***	**0.326***	Education		**0.431***	**0.398***
HCV			−0.123	HCV			−0.13

Note

*P<.05