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The Nature and Consequences of Cognitive Deficits among Tobacco Smokers with HIV: A Comparison to Tobacco Smokers without HIV

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Abstract

HIV-infected smokers lose more years of life to tobacco-related disease than HIV. Since neurocognitive deficits are common among those with HIV and are associated with smoking persistence, these deficits may be a unique barrier to smoking cessation among HIV-infected smokers. Documenting unique differences in and correlates of cognition among HIV-infected smokers is a critical step towards developing a population-specific tobacco cessation treatment. We compared neurocognitive function between HIV-infected (n=103) and HIV-uninfected smokers (n=70), accounting for demographic and smoking-related variables. We also evaluated whether HIV-related health outcomes (e.g., CD4 count, viral load, depression ratings, quality of life [QoL]) and HAART adherence were associated with cognition. Participants completed neurocognitive

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Conflict of Interest

Dr. Schnoll receives medication and placebo free from Pfizer and has provided consultation to Pfizer and GlaxoSmithKline. These companies had no involvement in this study.

Dr. Siegel has received grants and/or has acted as a consultant to Astellas, Merck, and Zynerva that is unrelated to the content of this manuscript.

Dr. Gross sits on a Data Safety and Management Board for a Pfizer drug treating inflammatory bowel disease that is unrelated to the contents of this manuscript.

tasks (N-back and Continuous Performance Task [CPT]) measuring working memory, attention, and processing speed, and intra-individual variability. Stepwise regression models were conducted and validated with resampling techniques. HIV-infected smokers performed worse than HIV-uninfected smokers on working memory, processing speed, and intra-individual variability (all $p < 0.01$). ROC analysis for the model including cognitive measures demonstrated 85% area under the curve, which indicates “good prediction” for distinguishing between HIV-infected and HIV-uninfected smokers. This was a significant improvement over the model including demographic and smoking-related variables only ($p = 0.0003$). Among HIV-infected smokers, neurocognitive performance was negatively associated with QoL and depression ratings. Smoking cessation interventions for HIV-infected smokers should consider cognitive neurorehabilitation as a potential strategy to decrease the likelihood of nicotine relapse and decrease tobacco-related morbidity in this population.

Keywords

Smoking cessation; HIV; Cognition; HIV-associated neurocognitive disorder; Tobacco Use

Introduction

Highly active antiretroviral therapy (HAART) has substantially improved survival rates among individuals with HIV (Deeken *et al*, 2012). Between 2001 and 2008, the percentage of adults living with HIV who are aged 50 or older increased from 17% to 31% and the rate continues to rise (Mahy *et al*, 2014). Although HAART enhances life expectancy and quality of life (QoL), HIV-infected individuals are increasingly vulnerable to non-AIDS-related diseases including cardiovascular disease, pulmonary disease, and non-HIV-associated malignancies (Rubinstein *et al*, 2014). Thus, addressing modifiable risk factors, such as tobacco use, among those with HIV/AIDS is a critical priority (Nahvi and Cooperman, 2009). In addition to cardiovascular disease, pulmonary disease and cancer, tobacco use increases the risk of opportunistic infections, and undermines HAART efficacy (Shirley *et al*, 2013). Indeed, HIV-infected smokers lose more life-years due to tobacco use than to HIV infection (Helleberg *et al*, 2013). Unfortunately, the smoking rate among HIV-infected individuals is more than twice the rate observed in the general population (Pacek and Cioe, 2015). Consequently, the development of smoking cessation interventions for HIV-infected smokers is an important priority.

To this end, assessing the role of neurocognitive deficits that may be unique to this population and pose a barrier to quitting smoking is essential. In the general population, smokers are at greater risk for neurocognitive deficits (Durazzo *et al*, 2012; Paul *et al*, 2006) and subsets of smokers, particularly those with psychiatric comorbidities characterized by neurocognitive deficits, may use nicotine to enhance cognitive function or attenuate withdrawal-related cognitive deficits (Ashare *et al*, 2014b; Lieberman *et al*, 2013). Indeed, resuming smoking ameliorates abstinence-induced cognitive deficits (Ashare *et al*, 2014a; Evans and Drobos, 2009). Importantly, deficits in cognitive function predict relapse above and beyond clinical measures (Loughead *et al*, 2015).

Cognitive deficits are a hallmark of HIV-1 infection (Weber *et al*, 2013) and are often referred to as HIV-associated neurocognitive disorder (HAND), which is classified as: HIV-associated dementia (HAD), mild neurocognitive disorder (MND), and asymptomatic neurocognitive impairment (ANI) (Antinori *et al*, 2007; Robertson and Yosief, 2014). While HAART has significantly reduced the incidence of HAD, MND and ANI persist. Indeed, 25–47% of HIV-infected people exhibit deficits in multiple cognitive domains including memory, verbal fluency, processing speed, and executive function (Heaton *et al*, 2015; Sacktor *et al*, 2016), which are associated with functional disabilities including unemployment, difficulty driving, and poor HAART adherence (Doyle *et al*, 2013). Although smoking may be negatively associated with cognition among HIV-infected individuals (Bryant *et al*, 2013; Schouten *et al*, 2014), few studies have assessed whether HIV-infected smokers experience greater cognitive deficits than their non-smoking counterparts.

The effects of HIV-1 infection on cognition may make HIV-infected smokers uniquely less able to quit smoking compared to HIV-uninfected smokers. Therefore, nicotine dependence interventions in the HIV-infected community may need to address cognitive impairment. This study was designed to: (1) examine whether neurocognitive performance differed between HIV-infected and HIV-uninfected smokers, accounting for demographic and smoking-related variables; and (2) identify which cognitive domains exhibit the greatest difference between the two samples. Secondly, we evaluated whether HIV-related health outcomes (e.g., CD4 count, viral load, depression ratings, QoL) and HAART adherence were associated with cognition. Documenting unique differences in and correlates of cognition among HIV-infected smokers is a critical step towards developing a population-specific tobacco cessation treatment.

Methods

Samples

HIV-infected Participants—Male and female participants over the age of 18 were recruited for a placebo-controlled clinical trial analyzing the effectiveness of varenicline for smoking cessation among those with HIV. Participants were recruited via media advertisements and from clinical sites, and all study visits were conducted at the University of Pennsylvania. For the present study, baseline data from 103 HIV-infected treatment-seeking cigarette smokers (≥ 5 cigarettes/day) from this parent trial were analyzed. Participants must have been diagnosed with HIV, have viral loads <1000 copies/mL, and CD4⁺ counts >200 cells/mm³, ALT/AST <2 times upper limit, and creatinine clearance >50 mL/min. Lifetime history of psychosis, suicide attempt, current or planned pregnancy, current use of smoking cessation medications, unstable or untreated alcohol/substance abuse, or non-fluency in English were exclusionary.

HIV-uninfected Participants—Male and female treatment-seeking smokers (≥ 10 cigarettes/day), ages 18–60 years old, were recruited from the community via advertisements for a placebo-controlled trial evaluating the effects of galantamine on short-term smoking cessation. After providing written informed consent, participants completed

an in-person eligibility screen including an expired breath carbon monoxide (CO) reading to confirm smoking status (< 10 ppm). Exclusion criteria included: current or planned pregnancy; low or borderline intelligence [Shipley IQ score < 90 , (Zachary, 2000)]; untreated alcohol/substance abuse; heart, kidney, or liver disease; uncontrolled hypertension; Alzheimer's disease; lifetime history of psychosis or bipolar disorder; suicide attempt; current major depression; and current use of smoking cessation or psychotropic medications, or contraindicated medications for galantamine.

Measures

Demographic and Smoking-related Measures—Self-reported demographics (e.g., age, sex, race) and smoking characteristics (e.g., cigarettes per day, number of years smoked, age at initiation) as well as the Fagerström Test for Nicotine Dependence [FTND (Heatherton *et al*, 1991)] were collected from both samples.

Cognitive Tasks

Continuous Performance Task (CPT): The Penn Continuous Performance Task (CPT) measures visual attention and vigilance (Kurtz *et al*, 2001). In this task, a series of red vertical and horizontal lines (7-segment displays) flash in a digital numeric frame (like a digital clock). The participant must press the spacebar whenever the lines form complete numbers or letters. The task is divided into two parts, each consisting of 180 trials (60 targets): first, the participant is asked to respond to numbers and then to letters. The discrimination index (i.e., the difference between the hit rate and the false alarm rate), which reflects the ability to distinguish between targets and foils (Snodgrass and Corwin, 1988), was calculated. The second outcome was median reaction time (RT) to correct targets (i.e., processing speed). We also computed the coefficient of variation (CV), which is the standard deviation (SD) of RT divided by the mean RT and reflects intra-individual variability in RT.

Visuospatial Working Memory N-Back Task: The current study employed a visuospatial working memory task based on prior research (Green *et al*, 2005). During the N-back, participants are instructed to remember the location of a stimulus, a gray circle approximately 5 cm in diameter, as it appears randomly in eight possible locations around the perimeter of a computer screen. The stimulus appears for 200 ms, followed by an interstimulus interval (ISI) of 2800 ms. A cross-hair remains visible during the stimulus presentation to cue participants to look at the center of the screen. The N-back includes four conditions of varying difficulty presented in pseudorandomized counterbalanced order: the 0-back, 1-back, 2-back, and 3-back. Each block consists of 50 trials with 15 targets per block. Participants respond only to targets (30% of stimuli) by pressing the spacebar. During the 0-back, participants are instructed to respond if the stimulus appears in a predetermined location (upper left corner of the screen). During the 1-back, participants are instructed to respond whenever the stimulus appears in the same location as the stimulus that immediately preceded it. During the 2- and 3-back conditions, participants are instructed to respond whenever the stimulus appears in the same location as the stimulus that preceded it by 2 or 3 trials, respectively. The primary outcomes for this task are the discrimination index (described above), median RT during correct targets, and CV (described above).

HIV-related Health Outcomes (HIV-infected Sample Only): For the HIV-infected sample, HIV-transmission category, HAART type and adherence information was collected. HAART adherence was a binary variable indicating whether any doses were missed in the past month (yes/no). Because efavirenz has documented adverse effects on cognition (Ma *et al*, 2016), we included a binary variable indicating current use of efavirenz. Laboratory values (HIV-RNA, CD4 count) were extracted from medical records. The HIV/AIDS-Targeted QoL (HAT-QoL) is a 34-item instrument assessing nine dimensions: overall function, sexual function, disclosure worries, health worries, financial worries, HIV mastery, life satisfaction, medication worries, and provider trust. All items use a “past 4 weeks” timeframe and a Likert-type scale from 1 (“all of the time”) to 5 (“none of the time”). Lower scores indicate lower QoL (Holmes and Shea, 1998). The Hospital Depression and Anxiety Scale (HADS) (Zigmond and Snaith, 1983), a 14-item self-report measure, assessed depression and anxiety ratings.

Data Analysis—Descriptive statistics were used to characterize the demographic, smoking history, disease-specific data, and neurocognitive performance for each sample. First, we conducted a forward stepwise regression (p -value 0.2 for removal, and 0.1 for entry) to select predictors for a logistic regression model (STATA logistic) to correctly classify group (HIV-uninfected vs. HIV-infected). Demographic variables (e.g., sex, age, race, and education) and smoking-related measures (FTND, cigarettes per day) were entered as baseline predictors. Neurocognitive measures (e.g., discrimination index, RT, and CV for the N-back and the CPT) were also included.

Following logistic regression, receiver operating characteristic (ROC) analysis was used to assess the predictive potential of the models (Steyerberg, 2008). Estimates of predictive accuracy are expressed as area under the ROC curve (AUC). The ROC curve is a plot of the sensitivity versus 1-specificity, representing the accuracy of a classification system, and provides a comparable metric across experiments (Bradley, 1997). Per ROC standards (Harrell *et al*, 1996), an AUC of .70–.80 indicates fair prediction; .80–.90 good prediction; and .90–1.0 excellent prediction. We then sought to validate the predictive models using two resampling methods. First, bootstrap procedures were used to create 1000 replicates of the data (random with replacement) and a stepwise regression (see above) was applied to assess model stability (Austin and Tu, 2004). The frequency of a variable’s inclusion in a model is considered an index of robustness, with those selected most often considered to be least influenced by outliers and error. To examine the model’s potential for prediction in new cases, we performed leave-one-out cross-validation (LOOCV) using root mean square error (RMSE) and mean absolute error (MAE) as indicators of goodness-of-fit (Steyerberg, 2008).

Secondarily, we sought to evaluate the association among HIV-related outcomes and neurocognition among HIV-infected smokers. We conducted separate stepwise regression models for each of the following outcomes: CD4 count, viral load, HAART adherence, the nine HAT-QoL domains, and HADS depression anxiety. Neurocognitive measures, demographic and smoking-related variables were included as predictors (see above). Current use of efavirenz was also included as a potential covariate.

Results

Sample Characteristics

Demographic and smoking-related characteristics for both samples are presented in Table 1. The samples were comparable with regard to sex, FTND, and cigarettes per day (p 's > 0.10). The HIV-infected sample was significantly older, started smoking at a younger age, exhibited lower baseline CO, was more likely to be African American, and reported lower levels of education and income (p 's < 0.10). All HIV-infected participants were stable on HAART and the most commonly reported medications were ritonavir (39%), emtricitabine/tenofovir disoproxil fumarate (TDF) (43%), darunavir (25%), and efavirenz/emtricitabine/TDF (21%).

Differences in Neurocognitive Function between HIV-infected and HIV-uninfected Smokers

Table 2 contains the means and SDs for all neurocognitive outcomes. The forward stepwise model retained education (OR=0.42, p =0.05, 95% CI: 0.18–0.98) and FTND (OR=0.78, p =0.04, 95% CI: 0.63–0.98), indicating that the HIV-infected sample reported lower levels of education and FTND scores. For neurocognitive measures, the stepwise model retained the N-back discrimination index (OR=0.001, p =0.001, 95% CI: 0.0002–0.05) and RT (OR=1.01, p <0.001, 95% CI: 1.0–1.01), and the CPT CV (OR=2.1x10⁸, p =0.002, 95% CI: 1419–3.2x10¹³), indicating worse cognitive performance among the HIV-infected sample, compared to the HIV-uninfected sample. For the ROC curve analysis, the model including all demographic and neurocognitive variables, produced a relatively high AUC of 85% corresponding to 76% correct classification rate (Figure 1). This model represents a significant improvement over demographic and smoking behavior predictors (age, FTND, race, education, sex, cigarettes per day) alone (AUC 70%, $X^2(1)=12.8$, p =0.0003).

Bootstrapping generated 1000 replicates of the data and conducted model selection on each replicate (Austin and Tu, 2004). The most frequent variables selected were (i.e., more than 500 times; number of times selected in parentheses): N-back RT (992), N-back discrimination index (934), CPT CV (893), education (661), and FTND (620). Notably, these were the same variables identified by the stepwise regression model. LOOCV further evaluated model performance. The RMSE and MAE for the full model (0.43 and 0.33, respectively) were lower than for the model including only demographic and smoking variables (0.48 and 0.44, respectively), indicating the full model yielded lower predictor error. LOOCV procedures yielded 85.6% AUC, corresponding to 79% correct classification. Thus, performance of both the training data and the LOOCV model would be characterized as “good prediction” (Hosmer and Lemeshow, 2000).

Association of Neurocognition with HIV-related Measures

For the model predicting CD4 count, being female (b =213.5, p =0.003) and having a lower discrimination index on the N-back (b =-567.1, p =0.01) were associated with higher CD4 count. For HADS depression, a lower discrimination index on the N-back was associated with higher depression ratings (b =-5.6, p =0.002). Likewise, being Caucasian (b =1.2, p =0.03), having a higher discrimination index on the N-back (b =3.6, p =0.02), and longer RT on the CPT (b =0.01, p =0.03) were associated with better HAT-QoL Health. For HAT-QoL

Satisfaction, fewer cigarettes per day was associated with higher QoL ($b=-0.10$, $p=0.006$). Lastly, lower education was associated with greater odds of missing a dose of HAART in the past month (OR=3.1, $p=0.01$, 95% CI 1.33–7.4). There were no significant predictors of viral load, HADS anxiety, or other domains of the HAT-QoL.

Discussion

This study compared cognitive performance between HIV-infected and HIV-uninfected smokers and identified the association of neurocognitive performance with HIV-related health outcomes. Previous studies with HIV-infected smokers and heavy drinking HIV-infected individuals showed that cigarette smoking was negatively associated with cognitive functioning (Bryant *et al*, 2013; Monnig *et al*, 2016). The present study extends these findings by demonstrating that, even after accounting for demographic and smoking-related characteristics, HIV-infected smokers performed worse on multiple cognitive domains. Moreover, among HIV-infected smokers, neurocognitive performance may be related to important health outcomes, including QoL and depression ratings.

First, compared to HIV-uninfected smokers, smokers with HIV performed worse on measures of working memory, processing speed, and intra-individual variability. This is consistent with evidence that, in the post-HAART era, the cognitive domains affected by HIV-infection are learning, memory, and executive function (Heaton *et al*, 2015; Sacktor *et al*, 2016). While the observed differences are modest, they may be important clinically. Indeed, slower processing speed is prospectively associated with greater cognitive decline (Cysique *et al*, 2010) and those who exhibit ANI may be more likely to progress to symptomatic HAND (Grant *et al*, 2014; Heaton *et al*, 2015). Additionally, intra-individual variability is higher among older HIV-infected individuals (Morgan *et al*, 2011). Thus, our finding that HIV-infected smokers exhibited greater intra-individual variability builds on evidence that inconsistent responding may be an important marker of cognitive decline (Hilborn *et al*, 2009) and highlights unique cognitive factors that may be important to address among HIV-infected smokers in conjunction with a smoking cessation intervention.

The current findings also suggest that several cognitive factors may be associated with HIV-related health outcomes. For instance, lower working memory performance was associated with higher depression ratings, lower health-related QoL, and higher CD4 count. Previous studies have found positive associations between successful cognitive aging and QoL (Moore *et al*, 2014). Although our findings are cross-sectional, it would be important to examine whether interventions to improve working memory could have downstream effects on QoL and depression ratings. Although lower nadir CD4 is reliably associated with worse cognitive function (Ellis *et al*, 2011), the relationship between neurocognition and current CD4 count is equivocal (Heaton *et al*, 2011). The current study did not assess nadir CD4, but our data suggest that better working memory may be associated with a lower current CD4 count. Although somewhat counterintuitive, some HAART medications (e.g., efavirenz) may have beneficial effects on CD4 count, while having adverse effects on neurocognition (Ma *et al*, 2016). Although we controlled for current use of efavirenz, the current sample was not large enough to evaluate differences in duration of use or by HAART type. This question should be addressed in future studies.

Because we controlled for demographic and smoking-related variables, the observed differences in cognitive performance may be caused by HIV-1 infection and the consequent neuronal damage via neurobiological mechanisms (Lindl *et al*, 2010). In the post-HAART era, persistent inflammation that does not completely reverse with viral suppression is thought to contribute to HAND (Hunt *et al*, 2016; Lederman *et al*, 2013). Tobacco smoking also induces inflammatory markers implicated in HAND (e.g., CRP, IL-6, MCP-1) (Stampfli and Anderson, 2009) and may compromise the integrity of the blood-brain barrier increasing the likelihood of monocyte transmigration into the brain and thus, enhancing the risk for neurodegeneration (Manda *et al*, 2010). Moreover, brain regions critical for neurocognitive function (e.g., prefrontal cortex and medial temporal lobe) are impacted by HAND (Hakkers *et al*, 2016) and smoking (Weiland *et al*, 2015). Thus, interactive effects between smoking and HIV-infection on inflammation and neural pathways suggest a potential mechanism underlying the differences in cognition between HIV-infected and HIV-uninfected smokers.

Controlling for other demographic and smoking-related variables, only education and nicotine dependence significantly differed between the groups. Notably, cognitive variables significantly improved the model's predictive validity to distinguish between HIV-infected and uninfected smokers, over and above demographic and smoking-related variables alone. With respect to HIV-related outcomes, women had a higher current CD4 count and Caucasians reported higher health-related QoL. Although previous studies found associations between cognition and HAART adherence (Thaler *et al*, 2015), in our study only lower education was associated with lower HAART adherence. Extending findings from the general population (Coste *et al*, 2014), we found that a higher smoking rate was associated with lower life satisfaction.

Several limitations warrant mention. First, these data were cross-sectional and potential mechanisms (e.g., neural substrates and inflammation) require further investigation. Second, including HIV-infected non-smokers would have allowed us to evaluate whether our findings were specific to smoking or HIV-infection. Third, although none of the HIV-uninfected smokers self-reported an HIV diagnosis, we did not have biological confirmation that these smokers were HIV negative, yet the <2% prevalence of HIV in Philadelphia makes it unlikely we misclassified HIV status (Philadelphia Department of Public Health, 2015). Lastly, even though we controlled for demographic and smoking-related differences, the samples were drawn from two clinical trials and some inclusion criteria differed between studies. Nevertheless, both trials only included daily smokers seeking treatment to quit smoking and both samples had comparable levels of nicotine dependence and smoking rate.

In summary, this study shows that HIV-infected smokers exhibit significantly worse working memory and processing speed and greater variability in response time compared to HIV-uninfected smokers. These cognitive measures may be related to important HIV-related health outcomes and may help identify smokers most likely to benefit from a treatment targeting cognition. Cognition has been identified as an important target for smoking cessation, particularly for those vulnerable to cognitive deficits (Ashare and Schmidt, 2014). Cognitive neurorehabilitation interventions (Weber *et al*, 2013) and cognitive enhancing medications (e.g., varenicline) (Patterson *et al*, 2009) might be beneficial additions to tobacco cessation programs for HIV-infected smokers, perhaps with extended treatment to

ensure enhanced cognitive function and reduced relapse risk. It is imperative that future studies with HIV-infected smokers examine treatment-related and withdrawal-related changes in cognition and relapse rates to further improve the health of this population.

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Figure 1.

ROC curves for two predictive models of HIV status. The full model (blue) includes demographic, smoking, and neurocognitive variables, yielding an AUC of 85%. Smoking and demographic predictors alone (red) achieved an AUC of 70% (red).

Table 1

Demographic and smoking characteristics of HIV-uninfected and HIV-infected samples.

Variable	HIV-uninfected (n=70)		HIV-infected (n=103)		p
	Mean	SD	Mean	SD	
Age	42.7	11.0	47.9	9.6	0.001
Cigarettes per day	16.4	6.0	14.7	8.0	0.12
FTND	5.2	1.8	5.0	1.8	0.35
CO at baseline (ppm)	21.1	9.8	15.8	10.0	0.001
Age smoking initiation (years)	18.0	4.3	16.4	0.51	0.03
Longest quit attempt (days) ^a	277	63	307	63	0.75
Plasma HIV RNA level [viral load (copies/mL)] ^b	N/A	N/A	1.5	0.30	
Plasma CD4 Count (cells/mm ³)	N/A	N/A	689.9	323.7	
Time since HIV diagnosis (months)	N/A	N/A	183.3	100.1	
	%	Count	%	Count	
Sex (Female)	36%	25	27%	28	0.23
Mode of Transmission					N/A
Sex	N/A	N/A	91%	98	
Injection Drug Use	N/A	N/A	5%	5	
Unknown	N/A	N/A	4%	4	
HAART Adherence					N/A
Missed a dose in last month	N/A	N/A	35%	35	
Current use of efavirenz	N/A	N/A	22%	23	N/A
Race					0.05
African American	60%	42	79%	81	
White	29%	20	17%	17	
More than one race	7%	5	2%	2	
Unknown	4%	3	3%	3	
Education					0.007
Some high school	3%	2	18%	19	
High school or GED	29%	20	33%	34	
Some college/technical school	47%	33	30%	31	

Variable	HIV-uninfected (n=70)		HIV-infected (n=103)		p
	Mean	SD	Mean	SD	
College graduate or beyond	21%	15	18%	19	< 0.001
Income ^c					
< \$20,000	41%	29	74%	76	
\$20,000 – \$35,000	21%	15	16%	16	
\$35,001 – \$50,000	21%	15	5%	5	
\$50,001 – \$75,000	7%	5	5%	5	
> \$75,000	6%	4	1%	1	
24-hour quit attempt (yes)	74%	52	73%	75	0.8

Note.

^aOnly individuals who reported having a quit attempt lasting at least 24 hours were included (HIV- n=52, HIV+ n=75);

^bbased on log 10 transformation;

^cTwo individuals in the HIV-uninfected sample refused to answer income question.

Table 2

N-back and CPT Performance for HIV-infected and –uninfected Samples

Measure	HIV-uninfected		HIV-infected	
	Mean	SD	Mean	SD
N-back Discrimination Index	0.72	0.09	0.62	0.14
N-back RT	616.8	111.7	728.2	174.5
N-back CV	0.25	0.05	0.24	0.07
CPT Discrimination Index	0.85	0.15	0.81	0.12
CPT RT	452.8	52.5	488.8	49.6
CPT CV	0.18	0.03	0.21	0.03

Note. Raw values are depicted for each task. CV = Coefficient of Variation