Title

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Journal

Journal of NeuroVirology, 26(6)

ISSN

1355-0284

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Publication Date

2020-12-01

DOI

10.1007/s13365-020-00878-5

Peer reviewed

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Journal of NeuroVirology

ISSN 1355-0284

J. Neurovirol.
DOI 10.1007/s13365-020-00878-5

Springer

Journal of NeuroVirology
https://doi.org/10.1007/s13365-020-00878-5

Association of HIV serostatus and metabolic syndrome with neurobehavioral disturbances

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Received: 7 January 2020 / Revised: 9 June 2020 / Accepted: 3 July 2020

Abstract

Metabolic syndrome (MetS), a constellation of related metabolic risk factors, is a common comorbidity associated with cognitive difficulty in people living with HIV (PLWH). Neurobehavioral disturbances (e.g., behavioral manifestations of frontal-subcortical dysfunction) are also prevalent in HIV, yet the role MetS might play in HIV-associated neurobehavioral disturbances is unknown. Thus, we examined the link between MetS and neurobehavioral disturbances in PLWH. Participants included 215 adults (117 PLWH, 98 HIV-uninfected), aged 36 to 65 years, from a cohort study at the University of California San Diego. Using the Frontal Systems Behavior Scale, we captured neurobehavioral disturbances (apathy, disinhibition, and executive dysfunction). MetS was defined by the National Cholesterol Education Program's Adult Treatment Panel-III criteria. Covariates examined included demographic, neurocognitive impairment, and psychiatric characteristics. When controlling for relevant covariates, both HIV serostatus and MetS were independently associated with greater apathy and executive dysfunction. HIV, but not MetS, was associated with greater disinhibition. The present findings suggest an additive effect of HIV and MetS on specific neurobehavioral disturbances (apathy and executive dysfunction), underscoring the importance of identifying and treating both HIV and MetS to lessen central nervous system burden among PLWH.

Keywords HIV/AIDS · Apathy · Executive dysfunction · Neurobehavioral signs and symptoms · Metabolic risk factors

Introduction

The discovery and use of combination antiretroviral therapy (ART) have resulted in reductions in HIV-related deaths and increased life expectancy among people living with HIV (PLWH) (Deeks et al. 2013; Gallant et al. 2017). Whereas continuous access and adherence to ART effectively prevents AIDS-related illnesses among PLWH, it does not fully restore immune health. Increased life expectancy comes with increased exposure to chronic inflammation and immune activation, likely resulting from both HIV disease and ART (Deeks et al. 2013; Gallant et al. 2017; Martin-Iguacel et al. 2016). For example, research has shown a strong association between lipid disorders and insulin intolerance and the use of specific ART regimens, such as protease inhibitors (PIs) (da Cunha et al. 2015). Chronic inflammation and immune activation potentially predispose PLWH to greater risk for premature and accentuated aging, making prevention and treatment of comorbidities an important

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Published online: 30 July 2020

component of HIV-related care (Pathai et al. 2013). Specifically, the three most common comorbidities for PLWH are hypertension, hyperlipidemia, and endocrine disease (including diabetes mellitus), which are all components of metabolic syndrome (MetS; Gallant et al. 2017).

MetS is conceptualized as a constellation of interrelated metabolic risk factors associated with an increased risk of developing cardiovascular disease (Grundy et al. 2005; Huang 2009; National Cholesterol Education Program (NCEP): Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults 2002). MetS is defined differently by various organizations, but generally includes visceral obesity, hypertension, endothelial dysfunction, atherogenic dyslipidemia, and insulin resistance (Saklayen 2018). MetS is common in the USA, with approximately 34–35% of adults aged 18 years or older in the general population falling within the clinical criteria, and greater prevalence of MetS is observed with increasing age (Aguilar et al. 2015; Moore et al. 2017a). Furthermore, MetS has also been consistently linked to neurocognitive dysfunction and brain abnormalities (Alcorn et al. 2017; Farooqui et al. 2012; Yaffe et al. 2004; Yates et al. 2012).

Among PLWH, MetS is highly prevalent (Jacobson et al. 2006; Martin-Iguacel et al. 2016) and there is evidence that its impact on neurocognitive impairment might be even more notable among PLWH than in the general population (Yu et al. 2019), possibly because of the impact of MetS on blood–brain barrier integrity and systemic inflammation (Gustafson et al. 2007; Sattler et al. 2015). Aside from MetS, neurocognitive impairment is prevalent in HIV, occurring in approximately 40% of PLWH (Heaton et al. 2010). HIV infiltrates the central nervous system early in the course of disease, resulting in neurocognitive impairment, which is often mild to moderate in severity in the era of combination ART. Another manifestation of CNS dysfunction in HIV are neurobehavioral disturbances or changes in daily behavior indicative of problems with motivation, initiating and organizing behavioral responses, and regulating emotional and behavioral responses in appropriate contexts (Bonelli and Cummings 2007; Grace et al. 1999; Malloy and Grace 2005). These neurobehavioral disturbances have been empirically linked to frontal-subcortical dysregulation and central nervous system disease and may be present in the absence of neurocognitive impairment (Bonelli and Cummings 2007; Cummings 1993; Grace et al. 1999; Ready et al. 2003). Previous research has shown a consistent link between HIV serostatus and increased neurobehavioral disturbances, particularly increased apathy (e.g., diminished self-initiation, blunted affect), disinhibition (e.g., impulsivity and problems with self-regulation), and executive dysfunction (e.g., difficulties with successfully performing goal-driven behavior) (Castellon et al. 1998; Kamat et al. 2016a; Kamat et al. 2012; Marquine et al. 2014). However, no studies have investigated the role of MetS on neurobehavioral disturbances associated with HIV.

The main purpose of the present study was to examine the association between MetS and neurobehavioral disturbances in the context of HIV disease. Given prior findings by Yu et al. (2019), we hypothesized that there would be an interaction between HIV serostatus and MetS on neurobehavioral disturbances, such that the association between MetS and neurobehavioral disturbances would be stronger among PLWH than among a HIV-uninfected comparison group, even after controlling for significant demographic and psychiatric characteristics and neurocognitive impairment.

Methods

Participants

Participants included 215 adults (117 PLWH, 98 HIV-uninfected) enrolled in the baseline visit of the Multi-Dimensional Successful Aging among HIV-Infected Adults study conducted at the University of California San Diego (UCSD) HIV Neurobehavioral Research Program and the UCSD Sam and Rose Stein Institute for Research on Aging from 2013 to 2015 (Moore et al. 2018; Moore et al. 2017c; Rooney et al. 2019). Inclusion criteria included being between the ages of 36–65 years old, being fluent in English, and having the ability to provide informed consent. Exclusion criteria included the presence of a neurologic condition other than HIV known to impact cognitive functioning (e.g., Alzheimer's Disease), diagnosis of a psychotic condition that could impact neurocognitive test performance (e.g., schizophrenia), and having a positive urine toxicology screen on day of testing for an illicit substance other than cannabis. Confirmation testing for HIV serostatus was completed during the testing visit (Abbott RealTime HIV-1 Test n.d.). In order to be included in present analyses, participants had to have data available on the main variables of interest, i.e., MetS and neurobehavioral disturbances.

Procedure

The UCSD Institutional Review Board approved the study, and all participants provided written informed consent and were compensated for participating. Participants self-reported demographic characteristics (age, sex, race/ethnicity, and years of formal education) and completed a comprehensive neuropsychiatric and neuromedical evaluation in individual sessions conducted by trained study staff. Methodological details of this study have been previously published (Moore et al. 2018; Moore et al. 2017c; Rooney et al. 2019).

Measures

Neurobehavioral disturbances

Neurobehavioral disturbances were assessed via the 46-item self-report version of the Frontal Systems Behavior Scale (FrSBe) (Malloy and Grace 2005; Stout et al. 2003). Participants provide retrospective ratings of how often they experience specific neurobehavioral symptoms "before the illness or injury" (i.e., before HIV infection for PLWH and before age 20 for HIV-uninfected participants) and "at the present time" using a Likert-type scale ranging from 1 ("almost never") to 5 ("almost always"). The scale yields T-scores adjusted for demographics (age, education, and gender) for the entire scale and three subscales measuring apathy, disinhibition, and executive dysfunction. T-scores have a mean of 50 and a standard deviation of 10, and higher T-scores indicate greater reports of neurobehavioral disturbances, with a T-score of 65 and higher suggesting clinical neurobehavioral disturbance. Previous studies have reported good internal reliability and consistent factor structure of the FrSBe subscales (Malloy et al. 2007; Stout et al. 2003). Consistent with previous research (Marquine et al. 2014; Posada et al. 2010) present time FrSBe T-scores were used as the outcome of interest for the current study.

Metabolic syndrome (MetS)

MetS was defined via the NCEP ATP III criteria (National Cholesterol Education Program (NCEP): Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults 2002). NCEP identifies the presence of metabolic risk factors (i.e., elevated waist circumference, diabetes mellitus, elevated blood pressure, elevated triglycerides, and reduced high-density lipoprotein) via laboratory assessments (e.g., phlebotomy, anthropomorphic, and vital signs measurements) or current medication use (self-report and/or record review, e.g., metformin for diabetes mellitus). Identification of the presence of these metabolic risk factors via laboratory measurements are based on the following five criteria: (a) waist circumference > 102 cm (men) and > 88 cm (women); (b) triglycerides ≥ 150 mg/dL; (c) high-density lipoprotein (HDL) cholesterol < 40 mg/dL (men) and < 50 mg/dL (women); (d) blood pressure ≥ 130/85 mmHg; and (f) fasting glucose ≥ 100 mg/dL (National Cholesterol Education Program (NCEP): Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults 2002). For every metabolic risk indicator present, a point is given. Points are then summed to create a total score (range, 0–5). For the present analysis, having clinically identified MetS was defined as the presence of 3 or more metabolic risk factors (coded 0 = no clinical identification of MetS, 1 = clinical identification of MetS), per established criteria (National Cholesterol Education Program (NCEP): Expert Panel on Detection and Treatment of High Blood Cholesterol in Adults 2002).

Covariates

Covariates examined included neurocognitive impairment and demographic and psychiatric characteristics (see Table 1).

Neurocognitive impairment was assessed via a comprehensive neurocognitive test battery, which assessed seven neurocognitive domains (i.e., speed of information processing, learning, delayed recall, executive functioning, verbal fluency, working memory, and fine motor skills), see Heaton et al. (2010) for details on the specific test battery. Deficit scores for each of the measures in the battery were computed and averaged to create a global deficit score (GDS) that adjusted for age, education, sex, and race, as applicable, using published methods (Cherner et al. 2007; Heaton et al. 2004; Heaton et al. 2002; Norman et al. 2011). A standard cutoff score of ≥ 0.5 was applied to the GDS to classify individuals as neurocognitively impaired (Carey et al. 2004).

Psychiatric characteristics, including lifetime and current major depressive disorder (MDD) and substance use disorders (abuse or dependence), were assessed via the Composite of International Diagnostic Interview (CIDI) (World Health Organization 1997), which follows diagnostic criteria set forth by the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 2000). Presence of a substance use disorder was determined by meeting criteria for abuse or dependence for a substance (i.e., marijuana, alcohol, cocaine, hallucinogens, inhalants, opioids, phencyclidine, and sedatives). Given the relatively lower prevalence of certain substance use disorders in our sample, the following substances were collapsed into a variable "other substance use disorder": cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, and other drug use. Responses were binary coded for every question (coded 0 = no, 1 = yes).

HIV disease characteristics

Blood specimens were obtained from PLWH at the study visit to determine CD4+ T cell count and plasma HIV viral load. "Detectable" plasma HIV viral load was defined as greater than 50 copies of HIV per milliliter or less of blood. During a standardized research clinical interview, participant self-reported estimated duration of infection, AIDS status, ART regimen, nadir CD4 count (i.e., lowest CD4 count ever measured). These self-report data were collected during a standard neuromedical interview and corroborated with review of historical lab values. Categorization of current ART regimen drug classes included: protease inhibitors (PIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs),

Table 1 Descriptive characteristics of the study cohort by HIV serostatus

	PLWH ($n = 117$)	HIV-uninfected ($n = 98$)	*t* test	*df*	*p*
Age, *M* (*SD*)	51.0 (8.4)	51.1 (7.6)	0.13	213	.896
Education, *M* (*SD*)	14.1 (2.5)	15.0 (2.3)	2.76	231	.006
			LRT	*df*	*p*
Race/ethnicity (*%*)			7.58	3	.055
Non-Hispanic White	56.4%	68.4%			
Non-Hispanic Black	19.7%	13.3%			
Hispanic	17.1%	17.3%			
Other	6.8%	1.0%			
			X^2	*df*	*p*
Sex (% male)	83.8%	68.4%	7.08	1	.008
Neurocognitively impaired, (%)	40.2%	24.5%	5.92	1	.015
Psychiatric characteristics (*%*)					
Current major depression	11.2%	0.0%	11.69	1	.001
LT major depression	55.9%	19.4%	29.16	1	< .001
LT alcohol use disorder	54.0%	29.6%	12.74	1	< .001
LT cannabis use disorder	27.0%	17.3%	2.80	1	.094
LT methamphetamine use disorder	34.2%	0.0%	41.00	1	< .001
LT other substance use disorder	37.8%	18.4%	9.64	1	.002
HIV disease characteristics					
Duration of HIV disease (years), *Median* (*IQR*)	18.8 (10.7, 25.4)	–			–
Current CD4, *Median* (*IQR*)	638 (432, 853)	–			–
Nadir CD4, *Median* (*IQR*)	180 (45, 322)	–			–
AIDS (%)	61.5%	–			–
On ART (%)	95.7%	–			–
Detectable plasma HIV RNA (*%*)	8.7%	–			–
Current ART medication type					
Protease inhibitors (PIs)	50.4%	–			–
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	31.6%	–			–
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)	92.3%	–			–
Integrase Strand Transfer Inhibitors (InSTIs)	35.9%	–			–
Entry inhibitors	2.6%	–			–

PLWH people living with HIV, *LT* lifetime, *ART* antiretroviral therapy, *RNA* ribonucleic acid

LT any other drug use disorder includes usage of cocaine, hallucinogens, inhalants, opioids, phencyclidine, sedatives, and any other drugs (not including alcohol, cannabis, or methamphetamine)

Missing data on psychiatric characteristics for PLWH: $n = 1$ for current major depression and $n = 6$ for LT major depression, LT alcohol use disorder, LT Cannabis use disorder, LT methamphetamine use disorder, and LT other substance use disorder

nucleoside reverse transcriptase inhibitors (NRTIs), integrase strand transfer inhibitors (InSTIs), and entry inhibitors.

Statistical analyses

All statistical analyses were conducted using SPSS 24 (IBM Corp 2016) and JMP 11.0.0 (SAS Institute Inc. 1989-2019) and considered statistically significant at $p < .05$. Descriptive statistics were computed for FrsBe scores, MetS, demographic and psychiatric characteristics, neurocognitive impairment, and HIV disease characteristics. Group comparisons by HIV serostatus on demographic and psychiatric characteristics and neurocognitive impairment were conducted (independent sample *t* tests for continuous variables, chi-square tests and likelihood ratio tests for categorical variables). HIV serostatus and MetS group differences on FrsBe scores were also conducted via independent sample *t* tests.

In order to examine the potential interactive effect of HIV and MetS on neurobehavioral disturbances, we conducted a series of linear regression models with terms for HIV serostatus, MetS, and their interaction on each FrSBe subscale. In cases where the interaction term was not significant,

it was removed from the model. The independent and unique effect of HIV serostatus and MetS on each FrSBe subscale was then assessed by evaluating linear regression models that included terms for HIV serostatus, MetS, and relevant covariates. In order to adjust for relevant covariates while also obtaining a parsimonious model for each FrSBe subscale, we followed these steps: (a) identified sociodemographic and psychiatric variables in Table 1 that were associated with each FrSBe subscale at $p < .10$ via a series of univariate regression models; (b) entered variables identified in Step 1 of the linear regression models and applied a stepwise backwards selection method based on Akaike information criterion (AIC) to obtain a parsimonious model for each FrSBe subscale. Age, sex, and education were not considered as possible covariates as FrSBe T-scores are adjusted for those demographic factors.

Results

The overall sample, on average, was 51.0 ($SD = 8.0$) years old, 76.7% male, 61.9% non-Hispanic White race, and had an average of 14.5 ($SD = 2.4$) years of formal education. There was a higher proportion of males in the PLWH group, and the PLWH group had fewer years of formal education compared to the HIV-uninfected group (see Table 1). The PLWH group had significantly higher percentages of neurocognitive impairment compared to the HIV-uninfected control group. The PLWH group was also more likely to have current and lifetime MDD, and lifetime substance use disorders of all substances other than cannabis. The median duration of HIV disease was approximately 18.6 years with a current CD4 median of 638 (IQR = 432, 853). Almost all PLWH were currently on ART, with the two most common drug classes being NNRTIs (92.3%) and PIs (50.4%), and less than 10% of the entire HIV seropositive sample had detectable plasma HIV RNA.

When assessing metabolic risk factors, clinically identified MetS was significantly more likely in PLWH when compared to the HIV-uninfected group (see Table 2). Specifically, the PLWH group had statistically higher percentages of elevated triglycerides ($p = .002$) and diabetes mellitus ($p = .046$). While PLWH had higher percentages of elevated blood pressure and reduced HDL cholesterol, no significant group differences were evident. Additionally, no significant HIV serostatus group differences were found for elevated waist circumference.

Average FrSBs subscale T-scores by HIV serostatus and MetS were assessed (Fig. 1). On average, PLWH reported more apathy ($t\ (205.47) = -4.08$, $p < .001$, $d = .54$), disinhibition ($t\ (213) = -3.50$, $p = .001$, $d = .48$), and executive dysfunction ($t\ (213) = -4.24$, $p < .001$, $d = .58$) when compared to the HIV-uninfected comparison group. For MetS, a significant difference was seen for both apathy ($t\ (213) = -3.07$, $p = .002$, $d = .43$) and executive dysfunction subscales ($t\ (102.38) = -2.77$, $p = .007$, $d = .45$), but not for the disinhibition subscale ($t\ (213) = -1.66$, $p = .099$, $d = .25$).

Univariate regressions were conducted to determine significant covariates for each FrSBe subscale. Statistically significant covariates for apathy included lifetime MDD, neurocognitive impairment, and lifetime alcohol and methamphetamine use disorders. Significant covariates for disinhibition included ethnicity, lifetime MDD, and lifetime alcohol, cannabis, and methamphetamine use disorders. Lastly, for executive dysfunction, significant covariates include lifetime MDD, neurocognitive impairment, and lifetime alcohol, methamphetamine, and other substance use disorders.

Linear regression models for each FrSBe outcome with HIV serostatus, MetS, and a HIV by MetS interaction term was conducted. Non-significant HIV by MetS interactions were seen for apathy ($b = 2.65$, $SE = 5.57$, $p = .634$), disinhibition ($b = -1.30$, $SE = 5.16$, $p = .800$), and executive dysfunction ($b = -1.74$, $SE = 4.46$, $p = .697$). Linear regression models assessing main effects in the presence of meaningful covariates are depicted in Table 3. In Step 1, significant independent main effects for HIV serostatus and MetS were found for apathy and executive dysfunction, indicating an additive

Table 2 Percentage of Metabolic Risk Factors by HIV serostatus

	PLWH ($n = 117$)	HIV-uninfected ($n = 98$)	X^2	df	p
	%				
MetS	37.6	22.4	5.76	1	.016
Elevated triglycerides	39.3	19.4	10.04	1	.002
Elevated blood pressure	50.4	41.8	1.58	1	.208
Diabetes mellitus	26.5	15.3	3.97	1	.046
			LRT		p
Reduced HDL cholesterol	49.6	35.7	4.89	2	.087
Elevated waist circumference	40.2	51.0	2.76	2	.251

PLWH people living with HIV, *HIV−* HIV seronegative, *MetS* metabolic syndrome, *HDL* high-density lipoprotein

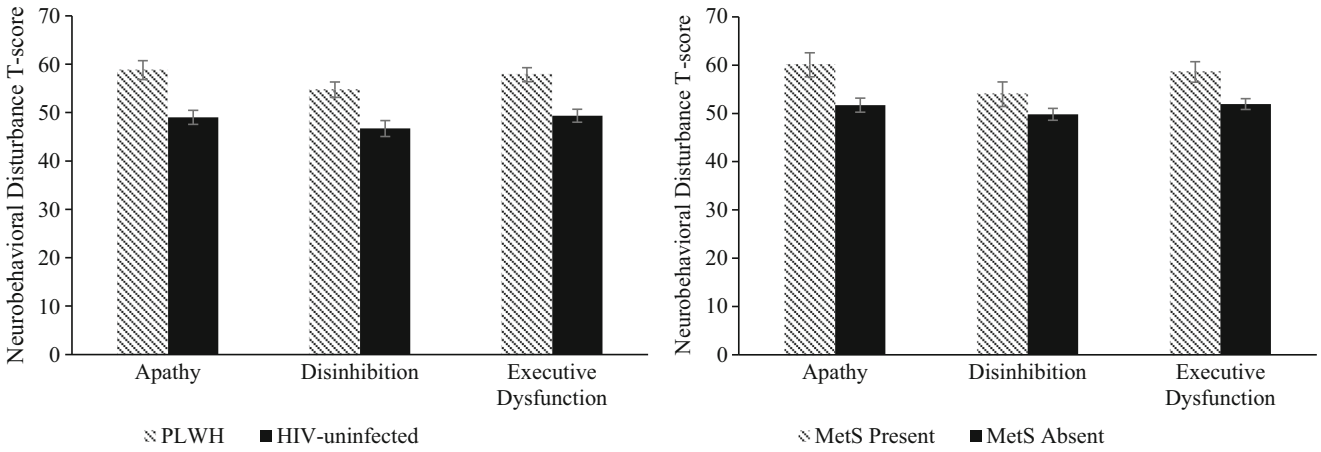

Fig. 1 FrSBe subscale mean T-scores by HIV serostatus and the clinical identification of MetS. Errors bars represent standard error of the sample mean. Higher T-scores indicate more reported problems with neurobehavioral disturbances

effect of HIV and MetS for these neurobehavioral disturbances. Only HIV serostatus was significantly associated with increased disinhibition.

Findings on the effects of HIV and MetS were largely similar, when significant covariates were included in the models (Step 2; Table 3), except the association of MetS with executive dysfunction which was marginally significant ($p = .055$). For apathy, lifetime MDD was the only covariate retained in the model, and it was associated with greater apathy. The disinhibition model covariates retained included lifetime MDD, lifetime cannabis use disorder, and ethnicity. Lifetime MDD ($p = .011$) and lifetime cannabis use disorder ($p = .027$) were associated with greater disinhibition. Furthermore, pairwise comparisons revealed that Hispanics showed greater disinhibition compared to Non-Hispanic Whites ($p = .009$), with no significant differences between Non-Hispanic Whites and Non-Hispanic Blacks ($p = .069$). Lastly, for executive dysfunction, the included covariates were lifetime MDD, neurocognitive impairment, and lifetime alcohol use disorder. Greater executive dysfunction was significantly associated with reporting lifetime MDD ($p = .018$), along with a marginally significant association with neurocognitive impairment ($p = .052$).

Table 3 HIV serostatus and MetS Associations with FrSBe subscales

	Apathy *b* (*SE*)	*p*	Disinhibition *b* (*SE*)	*p*	Executive dysfunction *b* (*SE*)	*p*
Step 1						
HIV serostatus	8.85 (2.50)	.001	7.57 (2.32)	.001	7.66 (2.00)	< .001
MetS	6.82 (2.70)	.012	2.85 (2.51)	.257	5.33 (2.16)	.015
Step 2						
HIV serostatus	6.70 (2.63)	.012	5.25 (2.49)	.036	4.38 (2.17)	.045
MetS	5.30 (2.66)	.047	---	---	4.12 (2.14)	.055
Neurocognitive impairment	---	---	---	---	4.11 (2.10)	.052
LT major depression	5.58 (2.67)	.038	6.60 (2.56)	.011	5.11 (2.15)	.018
LT alcohol use disorder	---	---	---	---	3.26 (2.03)	.110
LT cannabis use disorder	---	---	6.22 (2.78)	.027	---	---
Ethnicity (Non-Hispanic White vs. Hispanic)	---	---	8.23 (3.10)	.009	---	---
Ethnicity (Non-Hispanic White vs. Non-Hispanic Black)	---	---	− 5.70 (3.11)	.069	---	---

FrSBe Frontal Systems Behavior Scale, *MetS* metabolic syndrome, *LT* lifetime

Step 1 consists of a series of linear regressions with main effects of HIV serostatus and MetS for every subscale

Step 2 consists of a series of linear regressions with main effects of HIV serostatus and MetS while controlling for covariates using stepwise backwards selection method based on Akaike information criterion (AIC)

— Refers to variables that were not significant at the univariate level and not retained in the model after backwards selection

Discussion

MetS disproportionally impacts neurocognitive impairment, a marker of central nervous system dysfunction, among PLHIV compared to HIV-uninfected persons (Yu et al. 2019). Present findings revealed that similar interactive effects of HIV serostatus and MetS were not observed in the present sample on other behavioral manifestations associated with central nervous system dysfunction, i.e., neurobehavioral disturbances (self-reported apathy, disinhibition, and executive dysfunction). Instead, there was an additive effect such that being HIV seropositive and having a clinical identification of MetS were independently associated with greater apathy and executive dysfunction, and there was a significant effect of HIV serostatus only on disinhibition.

The presence of greater difficulties with neurobehavioral disturbances in PLWH compared to the HIV-uninfected comparison group aligns with previous research (Kamat et al. 2016a; Kamat et al. 2012). When looking at the frontal-subcortical circuits that may be affected, neuroimaging research has documented links between damage to the anterior cingulate cortex, dorsolateral prefrontal cortex, and orbital frontal cortex with difficulties with apathy, executive dysfunction, and disinhibition, respectively (Bonelli and Cummings 2007; Cummings 1993). Further, HIV-associated structural changes in both gray and white matter corresponding to these same areas have been documented (Archibald et al. 2014; Chang et al. 2001; Jernigan et al. 2011; Kuper et al. 2011). These cross-sectional findings inform the hypothesis that neurobehavioral disturbances seen in PLWH are associated with disease-related volume reduction and over-activation in comparison to HIV-uninfected comparison participants. These findings are of great interest not only from understanding how HIV affects the brain but also everyday functioning. For example, previous studies have shown associations between apathy and IADL decline, disability, and quality of life (Kamat et al. 2016b; Kamat et al. 2012; Shapiro et al. 2013); disinhibition, impulsivity, and risk-taking behaviors (Golub et al. 2010; Paydary et al. 2016); and executive dysfunction and ART medication adherence (Ettenhofer et al. 2009; Hinkin et al. 2004) and employment status (Cattie et al. 2012; Rabkin et al. 2004) in PLWH. Further research is needed to understand association directionality and how these associations progress with age over time.

While MetS and the related risk factors have been shown to be an important and unique predictor of neurocognitive change and decline in the general population (Alcorn et al. 2017; Farooqui et al. 2012; Siervo et al. 2014), little is known on how MetS is related to neurobehavioral disturbances. Previous research has shown that the presence of MetS is associated with increased odds of presenting with higher white matter hyperintensity volumes (OR 2.74; 95% CI 1.25, 6.03) and characterized by an anterior-posterior pattern of deterioration, such that greater deterioration is observed in the frontal lobe structures (Segura et al. 2009). Although not fully understood, several possible hypotheses on the mechanisms underlying the association between MetS and central nervous system dysfunction have been proposed, such as neuroinflammation, oxidative stress, abnormal brain lipid metabolism, altered cerebral hemodynamics, regional hypoperfusion, impaired cerebrovascular reactivity, and small vessel disease (Novak 2012; Yates et al. 2012). While the current findings are based on self-report, greater difficulties with apathy and executive dysfunction parallels the known associations between MetS and brain structure and function. Specifically, executive function, typically measured by neuropsychology test performance, appears to be particularly sensitive to the neurologic impact of MetS (Alcorn et al. 2017; Falkowski et al. 2014). Examination of individual components of MetS indicates that insulin resistance (Abbatecola et al. 2004), diabetes mellitus (Watari et al. 2008), obesity (Boeka and Lokken 2008), and hypertension (Schillerstrom et al. 2005) have been linked to impaired performance on executive function tasks.

Interestingly, HIV serostatus and MetS were independently associated with increased neurobehavioral disturbances within the same model, but there was no evidence of a statistical interaction. This is somewhat inconsistent with findings from Yu et al. (2019) who found evidence of an interaction on neurocognitive performance, such that association between MetS and neurocognitive impairment was stronger among PLWH than an HIV-uninfected comparison group. Yu et al. (2019) included a similar sample to ours, indicating that differences in participants' characteristics are unlikely to explain differential findings across studies. At least part of the reason for the apparent inconsistency might be that while neurocognitive impairment and neurobehavioral disturbances are both indicative of underlying central nervous system dysfunction, there is evidence that they can exist in isolation from one another (Bonelli and Cummings 2007; Cummings 1993; Grace et al. 1999; Malloy and Grace 2005). Neurobehavioral disturbances are usually associated with dysfunction to frontal-subcortical circuitry, while our index of global neurocognitive deficits includes various neurocognitive domains which are mediated by a variety of brain structures. Furthermore, prior findings indicate that the impact of MetS on neurocognition among PLWH is most notable in the domains of learning and motor functioning, with smaller effects on executive function (the hallmark neurocognitive deficit associated with frontal/subcortical circuitry) (Bonelli and Cummings 2007; Cummings 1993; Grace et al. 1999). Additionally, differences in HIV and MetS findings with neurobehavioral disturbances could allude to differential impacts on frontal-subcortical circuitry as there are both shared and segregated components to their structure (Bonelli and Cummings 2007) that can only be better investigated and understood using neuroimaging and longitudinal design.

Given the high prevalence of MetS and related negative health outcomes, efforts to prevent, treat, and possibly reverse the effects of MetS in middle-aged and older adults is of the greatest public health interest (Han and Lean 2016). Previous research has shown that diet influences MetS (Akbaraly et al. 2010; Esposito et al. 2004; Salas-Salvado et al. 2008). Additionally, increasing daily physical exercise and reducing physical inactivity (e.g., sedentary leisure time) in combination with a healthy diet has also shown to be effective in reducing metabolic risk and reversing MetS components (Bankoski et al. 2011; Rector et al. 2007). These lifestyle modifications may be particularly important for PLWH as previous research has shown varying levels of sedentary leisure time and physical inactivity (Vancampfort et al. 2018). For example, Moore et al. (2017b) showed using ecological momentary assessment in a sample of middle-aged PLWH that 32% of their time was spent engaging in passive leisure activity (e.g., watching television) compared to only 5% of their time which was spent engaging in physical exercise. Given the links between neurocognition and physical activity in PLWH (Fazeli et al. 2015; Fazeli et al. 2014; McDermott et al. 2017), more research is needed to see if interventions designed to increase physical activity (see Henry and Moore (2016) for an example) and improve diet may further reverse MetS components as well as the related-cognitive consequences.

Limitations of the present study include their cross-sectional nature. While we have discussed findings primarily in the direction of HIV and MetS impacting neurobehavioral disturbances, it is important to consider that the directionality of the findings cannot be ascertained in the context of the present cross-sectional analyses. It might be the case that pre-existing neurobehavioral disturbances resulted in persons being more likely to acquire HIV and/or MetS. Additionally, given the strong association between certain ART regimens (e.g., PIs, NNRTIs, NRTIs) and lipid and glucose metabolism in PLWH (da Cunha et al. 2015) and the high prevalence of these drug class types in our sample, further longitudinal investigation of lifetime and current ART regimens may provide more detail on the associations between HIV, MetS, and neurobehavioral disturbances. Another limitation included that neurobehavioral disturbances were based on self-report rather than informant report, observation, or performance-based tasks. While self-report might provide insight into daily behavior that may not be adequately captured or assessed with laboratory or clinic testing, self-report may also be confounded with bias, lack of awareness, and stigma of disease.

Implications and future directions

The current study revealed that both being HIV seropositive and having a clinical identification of MetS were independently associated with increased neurobehavioral disturbances in a sample of adults aging with and without HIV. These findings suggest that PLWH who also have a clinical identification of MetS may be at particularly increased risk for neurobehavioral disturbances, particularly apathy and executive dysfunction. Given the impact that neurobehavioral disturbances can have in everyday functioning (Cattie et al. 2012; Kamat et al. 2012), including adherence to a medical regimen (Ettenhofer et al. 2009; Hinkin et al. 2004), it might be important for healthcare providers to consider these behavioral manifestations in the healthcare management of PLWH so that they are better suited to cope with their comorbidities clinically and psychologically.

Acknowledgements The views expressed in this article are those of the authors and do not reflect the official policy or position of the Department of the Navy, Department of Defense, nor the United States Government. Portions of the data in this manuscript were presented at the HIV and Aging: From the Mitochondria to the Metropolis conference (April, 2019) Atlanta, GA. There are no conflicts of interest to report. This work was supported in part by the National Institutes of Health (R01MH099987, R25MH108389 [Sustained Training on Aging and HIV Research; STAHR], P30AG059299, K23MH105297, T32 DA031098, P30MH062512 [HIV Neurobehavioral Research Center; HNRC]) and the UC San Diego Sam and Rose Stein Institute for Research on Aging at the University of Calfornia San Diego.

*The San Diego HIV Neurobehavioral Research Center (HNRC) group is affiliated with the University of California, San Diego, the Naval Hospital, San Diego, and the Veterans Affairs San Diego Healthcare System, and includes Director: Robert K. Heaton, Ph.D.; Co-Director: Igor Grant, M.D.; Associate Directors: J. Hampton Atkinson, M.D., Ronald J. Ellis, M.D., Ph.D., and Scott Letendre, M.D.; Center Manager: Jennifer Iudicello, Ph.D.; Donald Franklin, Jr.; Melanie Sherman; NeuroAssessment Core: Ronald J. Ellis, M.D., Ph.D. (P.I.), Scott Letendre, M.D., Thomas D. Marcotte, Ph.D, Christine Fennema-Notestine, Ph.D., Debra Rosario, M.P.H., Matthew Dawson; NeuroBiology Core: Cristian Achim, M.D., Ph.D. (P.I.), Ana Sanchez, Ph.D., Adam Fields, Ph.D.; NeuroGerm Core: Sara Gianella Weibel, M.D. (P.I.), David M. Smith, M.D., Rob Knight, Ph.D., Scott Peterson, Ph.D.; Developmental Core: Scott Letendre, M.D. (P.I.), J. Allen McCutchan; Participant Accrual and Retention Unit: J. Hampton Atkinson, M.D. (P.I.) Susan Little, M.D., Jennifer Marquie-Beck, M.P.H.; Data Management and Information Systems Unit: Lucila Ohno-Machado, Ph.D. (P.I.), Clint Cushman; Statistics Unit: Ian Abramson, Ph.D. (P.I.), Florin Vaida, Ph.D. (Co-PI), Anya Umlauf, M.S., Bin Tang, M.S.

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