UC San Diego
UC San Diego Previously Published Works

Title

Effects of trauma, economic hardship, and stress on neurocognition and everyday function in HIV.

Permalink

https://escholarship.org/uc/item/1xx17883

Journal

Health psychology : official journal of the Division of Health Psychology, American Psychological Association, 38(1)

ISSN

0278-6133

Authors

Watson, Caitlin Wei-Ming
Sundermann, Erin E
Hussain, Mariam A
et al.

Publication Date

2019

DOI

10.1037/hea0000688

Peer reviewed

Health Psychology

Effects of trauma, economic hardship, and stress on neurocognition and everyday function in HIV

--Manuscript Draft--

Manuscript Number:	
Full Title:	Effects of trauma, economic hardship, and stress on neurocognition and everyday function in HIV
Abstract:	Objective: The causes of impairment in cognition and everyday functioning among people living and aging with HIV are multifactorial. Exposure to stress and trauma can result in cognitive deficits via activation of neurological and other biological mechanisms. Methods: 122 persons living with HIV (PLWH) and 95 persons without HIV (HIV-), between 35-65 years, completed four questionnaires that were used to comprise a trauma, economic hardship (food insecurity and low socioeconomic status), and stress composite variable (TES). Participants also completed a comprehensive neuropsychological battery and standardized self-reports of activities of daily living (ADLs). We examined the independent and interactive effects of TES and HIV+ status on neurocognitive performance and ADL declines. Results: PLWH had more traumatic events, more food insecurity, lower socioeconomic status, and higher perceived stress compared to HIV- individuals (all ps<.0001). Among PLWH, a higher TES score was associated with worse executive functioning (p=.009), worse learning (p=.008), worse working memory (p=.005), and more ADL declines (p<.0001), even after controlling for relevant demographic, psychiatric, substance use, and HIV disease covariates. Conversely, no significant relationships were observed between TES and cognitive domains nor ADL declines among individuals without HIV. Conclusions: A composite score of trauma, economic hardship, and stress was significantly associated with worse cognitive performance and functional declines among PLWH. These adverse experiences may contribute to neurocognitive and daily functioning difficulties commonly observed among PLWH. Longitudinal studies are needed to elucidate the relationships between economic/psychosocial adversity and cognitive/functional outcomes over time, and examine potential mediators, such as inflammatory biomarkers.
Article Type:	Article
Corresponding Author:	David J Moore, Ph.D. University of California, San Diego San Diego, CA UNITED STATES
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	University of California, San Diego
Corresponding Author's Secondary Institution:	
First Author:	Caitlin Wei-Ming Watson, B.A.
First Author Secondary Information:	
Order of Authors:	Caitlin Wei-Ming Watson, B.A.
	Erin E Sundermann, Ph.D.
	Mariam A Hussain, B.S.
	Anya Umlauf, M.S.

	April D Thames, Ph.D.
	Raeanne C Moore, Ph.D.
	Scott L Letendre, M.D.
	Dilip V Jeste, M.D.
	Erin E Morgan, Ph.D.
	David J Moore, Ph.D.

Order of Authors Secondary Information:	
Keywords:	PLWH; aging; socioeconomic status; food insecurity; cognition; activities of daily living
Manuscript Classifications:	Adults; Aging; AIDS/HIV; Cognitive function; Posttraumatic stress; Poverty; Psychosomatics; Quality of life; Social factors influencing health; Socioeconomic status; Stress and health
Suggested Reviewers:	Uraina S. Clark, Ph.D. Assistant Professor, Icahn School of Medicine at Mount Sinai Tisch Cancer Institute uraina.clark@mssm.edu Researches adversity (including chronic stress) and neuropsychological functioning and impairment in people living with HIV.
	Gretchen N. Neigh, Ph.D. Associate Professor, Virginia Commonwealth University gretchen.mccandless@vcuhealth.org Researches stress and cognition in HIV
	Robert H. Paul, Ph.D. Assistant Professor, University of Missouri-St. Louis paulro@umsl.edu Neuropsychologist with expertise in HIV and aging

UNIVERSITY OF CALIFORNIA, SAN DIEGO   UCSD

BERKELEY • DAVIS • IRVINE • LOS ANGELES • MERCED • RIVERSIDE • SAN DIEGO • SAN FRANCISCO   SANTA BARBARA • SANTA CRUZ

DAVID J. MOORE, PH.D.   VOICE: 619.543.5093
HIV NEUROBEHAVIORAL RESEARCH PROGRAM   FAX: 619.543.1235
220 DICKINSON ST., SUITE B   WEBSITE: hnrp.hivresearch.ucsd.edu
MAIL CODE 8231   EMAIL: djmoore@ucsd.edu
SAN DIEGO, CA 92103-8231

November 6th, 2017

Kenneth E. Freedland, Ph.D.
Behavioral Medicine Center
Washington University School of Medicine
4320 Forest Park Avenue, Suite 301
St. Louis, MO 63108
Email: freedlak@wustl.edu
Editor: Health Psychology

Re: New Manuscript Submission

Dear Dr. Freedland:

Attached is a manuscript titled "Effects of trauma, economic hardship, and stress on neurocognition and everyday function in HIV," submitted for consideration in *Health Psychology*. None of the original material contained in the manuscript has been submitted for consideration nor will any of it be published elsewhere except in abstract form in connection with scientific meetings.

In this paper, we present novel research on the relationship of trauma, economic hardship (food insecurity and low socioeconomic status), and stress on neurocognitive and everyday functioning outcomes in adults, between the ages of 35-65 years, living with and without HIV (N = 217). Results indicated that a composite score of trauma, economic hardship, and stress was significantly associated with worse cognitive performance and functional declines among people living with HIV, but not in individuals without HIV. Findings suggest that multiple adverse experiences may contribute to commonly observed neurocognitive and daily functioning difficulties in PLWH. Given high rates of trauma, poverty, sexual and physical abuse in PLWH, these findings have high clinical relevance, and suggest that screenings for traumatic, stressful, and other adverse events and resources for coping and breaking the cycle of exposure to these experiences should be a part of standard HIV care. This manuscript meets *Health Psychology* publishing priorities as outlined by your 2017 article "A New Era for *Health Psychology*" as our work has clear clinical and public health significance in a population living with HIV infection, and points to future translational work which will examine markers of physical health such as inflammatory biomarkers.

Participants came from the Multi-Dimensional Successful Aging among Adults living with HIV study at University of California San Diego, aimed at investigating the relationship of positive psychological factors and aging biomarkers to different domains of successful aging in PLWH and individuals without HIV. Papers focused on valid assessment of everyday functioning, positive psychological traits and

successful aging, grit and global neurocognitive performance, as well as frailty and neurocognitive impairment are currently under review or have been accepted for publication. Planned papers include those that focus on inflammatory biomarkers and metabolic syndrome in neurocognitive impairment, physical activity and nutrition in HIV, and the relation of positive psychological traits to HIV disease outcomes. Our manuscript has a distinct focus, and provides a significant scientific contribution, separate from papers currently under review and those planned for the future.

We followed APA ethical standards in conducting this study and have no conflicts of interest to report. All authors have read and approved of this submission, in addition to the journal's instructions to authors, and have made a substantial contribution to the conception, design, gathering, analysis and/or interpretation of data and a contribution to the writing and intellectual content of the article; and acknowledge that they have exercised due care in ensuring the integrity of the work.

I will serve as corresponding author and will keep my colleagues informed as to the editorial progress of the manuscript. Please do not hesitate to contact me if revisions or clarifications are needed. Thank you for considering our work in *Health Psychology*.

Warm regards,

David J. Moore[2], Ph.D.
Associate Professor, Department of Psychiatry

Caitlin Wei-Ming Watson[1], Erin E. Sundermann[2], Mariam A. Hussain[1], Anya Umlauf[2], April D. Thames[3], Raeanne C. Moore[2,5], Scott L. Letendre[4], Dilip V. Jeste[2,6,7], & Erin E. Morgan[2]

[1]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology
[2]Department of Psychiatry, University of California San Diego
[3]University of California Los Angeles
[4]Department of Medicine, University of California San Diego
[5]VA San Diego Healthcare System
[6]Stein Institute for Research on Aging, University of California San Diego
[7]Department of Neuroscience, University of California San Diego

**Effects of trauma, economic hardship, and stress on neurocognition
and everyday function in HIV**

Caitlin Wei-Ming Watson[1], Erin E. Sundermann[2], Mariam A. Hussain[1], Anya Umlauf[2], April D. Thames[3], Raeanne C. Moore[2,5], Scott L. Letendre[4], Dilip V. Jeste[2,6,7], Erin E. Morgan[2], & David J. Moore[2]

[1]San Diego State University/University of California San Diego Joint Doctoral Program in Clinical Psychology, [2]Department of Psychiatry, University of California San Diego, [3]University of California Los Angeles, [4]Department of Medicine, University of California San Diego, [5]VA San Diego Healthcare System, [6]Stein Institute for Research on Aging, University of California San Diego, [7]Department of Neuroscience, University of California San Diego

Manuscript page count: 29
Abstract word count: 249
Tables: 1
Figures: 5

Corresponding author:
David J. Moore, PhD
Department of Psychiatry
University of California San Diego
220 Dickinson Drive, Suite B (8231)
San Diego, CA 92103-8231
Email: djmoore@ucsd.edu
Phone: 619-543-5093
Fax: 619-543-1235

Abstract

Objective: The causes of impairment in cognition and everyday functioning among people living and aging with HIV are multifactorial. Exposure to stress and trauma can result in cognitive deficits via activation of neurological and other biological mechanisms.

Methods: 122 persons living with HIV (PLWH) and 95 persons without HIV (HIV-), between 35-65 years, completed four questionnaires that were used to comprise a trauma, economic hardship (food insecurity and low socioeconomic status), and stress composite variable (TES). Participants also completed a comprehensive neuropsychological battery and standardized self-reports of activities of daily living (ADLs). We examined the independent and interactive effects of TES and HIV+ status on neurocognitive performance and ADL declines.

Results: PLWH had more traumatic events, more food insecurity, lower socioeconomic status, and higher perceived stress compared to HIV- individuals (all *ps*<.0001). Among PLWH, a higher TES score was associated with worse executive functioning (*p*=.009), worse learning (*p*=.008), worse working memory (*p*=.005), and more ADL declines (*p*<.0001), even after controlling for relevant demographic, psychiatric, substance use, and HIV disease covariates. Conversely, no significant relationships were observed between TES and cognitive domains nor ADL declines among individuals without HIV.

Conclusions: A composite score of trauma, economic hardship, and stress was significantly associated with worse cognitive performance and functional declines among PLWH. These adverse experiences may contribute to neurocognitive and daily functioning difficulties commonly observed among PLWH. Longitudinal studies are needed to elucidate the relationships between economic/psychosocial adversity and cognitive/functional outcomes over time, and examine potential mediators, such as inflammatory biomarkers.

Keywords: PLWH, aging, socioeconomic status, food insecurity, cognition, activities of daily living

Introduction

Over 35 million people worldwide live with human immunodeficiency virus (HIV), and 1.2 million of these people live in the United States. Since the development of combination antiretroviral therapy (cART), HIV-associated mortality has decreased in the United States, such that the lifespan of people living with HIV (PLWH) with reliable access to cART is comparable to those without HIV (Samji et al., 2013). Despite these advances in the medical management of HIV disease, the central nervous system remains vulnerable. In fact, HIV targets the CNS within days after infection leading to neurological, behavioral, and cognitive complications (Brew, Sidtis, Petito, & Price, 1988; McArthur, 1994). Even in the current cART era, mild neurocognitive deficits are observed in about 45% of PLWH, particularly in the domains of executive function, learning, and memory (Heaton et al., 2011). Neuroimaging studies suggest that functional and structural abnormalities in subcortical regions underlie these cognitive deficits (Castelo, Sherman, Courtney, Melrose, & Stern, 2006; Maki et al., 2009). Neurocognitive impairment among PLWH is clinically meaningful because it is known to adversely affect daily functioning, conferring an increased risk of poor medication management (Heaton et al., 2004; Hinkin et al., 2004), impaired driving ability (Marcotte et al., 1999), problems in employment (Rabkin, McElhiney, Ferrando, Van Gorp, & Lin, 2004; van Gorp, Baerwald, Ferrando, McElhiney, & Rabkin, 1999), and early mortality (Vivithanaporn et al., 2010). As the HIV+ population ages, understanding and addressing HIV-associated comorbidities that impact cognitive performance and everyday functioning is critical to overall healthcare for PLWH.

Multiple adverse experiences such as childhood trauma, sexual abuse, physical violence, unemployment, and poverty (Brief et al., 2004; Machtinger, Wilson, Haberer, & Weiss, 2012;

Spies et al., 2012) are highly prevalent among PLWH (Pence et al., 2007; Whetten et al., 2006) and have known CNS consequences. For example, estimates of sexual and/or physical abuse in PLWH range from 30% to over 50% (Pence et al., 2007; Whetten et al., 2006) Whereas the physiological response to acute stress is typically adaptive, chronically-elevated stress exposure can disturb brain development and function, and increase risk of psychiatric disease (De Kloet, Joëls, & Holsboer, 2005; Kessler et al., 2010; McEwen, 2000; Radley, Morilak, Viau, & Campeau, 2015; Scott, McLaughlin, Smith, & Ellis, 2012). Chronic exposure to stress and stress hormones, glucocorticoids, can hinder immune mechanisms and amplify inflammation in the CNS and, furthermore, exacerbate injury-induced neuronal death (Dinkel, Ogle, & Sapolsky, 2002; Sorrells, Caso, Munhoz, & Sapolsky, 2009). Chronic stress in healthy adults is linked to structural and functional alterations in the hippocampus and prefrontal cortex (Lupien, McEwen, Gunnar, & Heim, 2009), and poorer memory recall ability (Lupien et al., 1997; Wilding, Andrews, & Hejdenberg, 2007).

Due to the overlap in the inflammatory and immune mechanisms shown to be affected by stress and HIV, traumatic and stressful experiences may contribute to or compound the likelihood of CNS injury via this pathway in PLWH (Valdez, Rubin, & Neigh, 2016). Thus, PLWH with a history of trauma and adversity may be at increased risk for neurocognitive impairment and decreased functional capacity. Among men living with HIV, a previous study found that stressful life events were related to worse executive functioning, attention, and processing speed (Pukay-Martin, Cristiani, Saveanu, & Bornstein, 2003). In women living with HIV, high levels of self-reported stress were associated with verbal memory deficits, as well as prefrontal cortex structural and functional deficits (Rubin et al., 2015; Rubin et al., 2016a; Rubin et al., 2016b). Conversely, high stress was not associated with verbal memory performance in

women without HIV, suggesting that stress may be particularly deleterious to cognitive function in the context of HIV. Another recent study found that PLWH (85% men) with higher levels of social adversity showed reduced volumes of subcortical structures (right amygdala and left hippocampus) and worse learning/memory performance, and these findings did not extend to the HIV- group (Thames et al., 2017). Stress, emotional reactivity, and avoidant coping behaviors are related to important daily functioning behaviors such as medication nonadherence among PLWH (Martinez et al., 2012).

Although multiple studies have examined the effects of stress on cognitive function within cohorts of PLWH or individuals without HIV, few have directly compared the effects between serostatus groups while examining the combined effects of multiple traumatic and stressful experiences, or included standardized measures of daily functional abilities. In the present study, we investigated whether a composite measure of multiple adverse experiences including trauma, economic hardship, and stress (TES) exerts a negative impact on cognitive and everyday function in a cohort of adults living with and without HIV. We hypothesized that PLWH would experience more trauma, economic hardship, and stress than their HIV- counterparts. Furthermore, we hypothesized that elevated TES would relate to worse cognitive function and everyday function in both serostatus groups, but the magnitude of the association would be greater for PLWH compared to their HIV- counterparts, after controlling for established predictors of cognitive and functional status.

Methods

Study cohort. Participants were 122 PLWH and 95 adults without HIV from the Multi-Dimensional Successful Aging among Adults living with HIV study conducted at the University

of California San Diego (UCSD). This study utilized cross-sectional data from the first study visit. The UCSD Institutional Review Board approved this study, and all participants provided written, informed consent. Exclusion criteria were minimal in order to enroll a representative cohort of PLWH and HIV- adults, and included: (1) diagnosis of a psychotic disorder (e.g., schizophrenia) or mood disorder with psychotic features; (2) presence of a significant neurological condition (beyond HIV infection) known to impact cognitive functioning (e.g., Alzheimer's disease, stroke, traumatic brain injury); (3) positive urine toxicology on the day of testing. An HIV/HCV finger stick point of care test (Abbott RealTi*me* HIV-1 test, Abbott Laboratories, Illinois, USA) was used to test all participants for HIV infection. Of the participants who reported they were HIV- at screening, none tested positive for HIV. Study visits consisted of detailed neuromedical, psychosocial, and cognitive assessments, and specimen collection.

Demographic characteristics. Demographic information (age, years of education, gender, race and ethnicity) was obtained via self-report. Race and ethnicity were ascertained following NIH guidelines and consistent with the US Census Bureau methodology (Office of Management and Budget, 1997).

Trauma, economic hardship, and stress evaluation. Our TES composite variable was derived to capture three components of adversity: (1) traumatic events (social), (2) economic hardship: food insecurity and low socioeconomic status (SES) (structural), and (3) perceived stress (psychological). Traumatic events were assessed by the self-report Women's Health Initiative (WHI) Life Events Scale, which assesses traumatic events over the past year (Michael et al., 2009; Ruberman, Weinblatt, Goldberg, & Chaudhary, 1984). For our trauma variable, we included the following five items from this scale: (1) death of a spouse or partner, (2) major

problems with money, (3) a major accident, disaster, mugging, unwanted sexual experience, or robbery, (4) physical abuse by a family member or close friend, or (5) verbal abuse by a family member or close friend, for which the participant rated the event as moderately or very upsetting. In the overall cohort, the number of traumatic life events ranged from zero to five ($M = .6$, $SD = 1.0$). We categorized trauma as high when one or more of the five traumatic events were endorsed (38% of overall cohort). The economic hardship variable had two components: food insecurity and SES. Food insecurity was evaluated by endorsement of the statement "I don't always have enough money to buy the food I need" (20% of overall cohort). SES was assessed by the Hollingshead Index of Social Status (Hollingshead, 1975), a weighted average of years of education, current or longest held occupation, and total household income of the participant. We categorized SES as low when Hollingshead Index scores were in the bottom tertile (33% of overall cohort). The stress variable consisted of the Perceived Stress Scale (PSS-10) (Cohen, Kamarck, & Mermelstein, 1983; Cohen & Williamson, 1988), a widely-used, 10-item, self-report instrument that evaluates how stressful the respondent found situations in the past month. We categorized stress as high when PSS-10 scores were in the top tertile (33% of overall cohort), and low (low-to-moderate) when PSS-10 scores were in the bottom two tertiles, similar to previous research in PLWH (Massad et al., 2011; Rubin et al., 2015).

Following methods described by Troxel et al., 2003, each of the four indicators was dichotomized into "0" or "1" using the top or bottom 20-40% of the sample distribution (Thames et al., 2017; Williamson, Mahmood, Kuhn, & Thames, 2017). Our TES composite was the sum of the dichotomous values (trauma: 0 or 1; economic hardship – food insecurity: 0 or 1; economic hardship – low SES: 0 or 1; perceived stress: 0 or 1) into one score ranging from 0-4 to represent a cumulative index of adverse experiences related to trauma, economic hardship, and

stress. In the overall cohort, 32% had a score of 0, 30% had a score of 1, 23% had a score of 2, 11% had a score of 3, and 4% had a score of 4 on the TES composite. Figure 1 shows the distribution of TES by HIV status group.

…………………..…………[INSERT FIGURE 1 HERE] ……………...………………………

Neurocognitive evaluation. Participants completed a standardized, comprehensive neurocognitive battery including tests of executive function, learning, memory (delayed recall), working memory, verbal fluency, speed of information processing, and complex motor skills. The cognitive battery has been described in full detail previously (Heaton et al., 2004; Moore et al., 2017). Raw scores for each test were converted to T-scores adjusting for demographic characteristics (age, education, gender, race/ethnicity) and practice-effects when appropriate (Cysique et al., 2011; Heaton et al., 2010). Global and domain-specific continuous T-scores were used in our analyses.

Everyday functioning evaluation. All participants completed a modified version of the Activities of Daily Living (ADL) Scale (Lawton & Brody, 1969), a self-report measure used to assess an individual's level of independent functioning in a range of daily activities (Heaton et al., 2004). Participants rate their current and best (i.e., highest previous) level of functioning on 16 basic and instrumental everyday activities (housekeeping, home repairs, bathing, dressing, laundry, finances, shopping, grocery shopping, understanding reading material/TV, planning social activities, communication, medication management, transportation, cooking, child care, and work). For the current study, the summed total of domains on which declines were reported in current versus past functioning over the 16 ADLs was the everyday function outcome of interest ($M = 1.42$, $SD = 2.48$, *Range*=0-14) (Morgan, Woods, & Grant, 2012).

Psychiatric and substance use characteristics. To evaluate current and lifetime histories of major depressive disorder (MDD) and substance use disorders, the computer-assisted Composite International Diagnostic Interview (CIDI, v2.1) was administered. The CIDI is a computer-assisted, fully-structured interview that provides an assessment of alcohol, drug, and mental disorders using DSM–IV criteria (Wittchen et al., 1991).

HIV Disease characteristics. Among PLWH, participants underwent a comprehensive neuromedical evaluation that included assessment of medical history (including HIV history and treatment), and collection of blood samples. Severity of HIV disease was characterized by utilizing CD4+ T-cell counts (nadir and current), estimated duration of HIV disease, and AIDS/non-AIDS classification, and HIV RNA viral load, measured by reverse transcriptase-polymerase chair reaction (Abbott m2000 HIV 1,2; lower limit of quantitation 40 copies per milliliter).

Statistical analyses. Prior to conducting primary analyses, independent samples *t*-tests and Chi-square tests were used to compare HIV status groups on demographic, psychiatric, substance use, and clinical variables. Any variables that differed between the HIV+ and HIV-groups at $p < .1$ were added as covariates when analyzing the relationship between TES and cognitive/functional outcomes. Thus, we included gender, ethnicity, years of education, lifetime MDD, lifetime substance use disorder (except alcohol and cannabis), lifetime alcohol use ($p < .05$), and lifetime cannabis use ($p < .1$) in the models for cognition. We did not include current MDD as a covariate due to its low prevalence. For functional outcomes, we additionally included global neurocognitive impairment ($p < .1$) as a covariate. For PLWH-only models, any HIV disease characteristics that related to global cognition or ADL declines at $p < .1$ in univariable analyses were added as covariates. For our models in which a cognitive domain in PLWH was

the outcome variable, current CD4 count was included as an additional covariate, given that it was associated with global cognition at $p < .1$ in univariable analyses. For our model in which a functional outcome in PLWH was the outcome variable, estimated duration of HIV infection was included as an additional covariate, given that it was associated with ADL declines at $p < .1$ in univariable analyses.

We used multivariable linear regression analyses to examine the independent and interactive effects of the TES composite and HIV status on cognitive function and declines in activities of daily living. Separate univariable models were run for each of the seven cognitive domains and global cognition, and alpha was set at 0.006 (.05/8). We pursued multivariable analyses only for those cognitive domains that showed a significant relationship with TES in univariable models, and in multivariable analyses, alpha was set at 0.017 (.05/3), based on the number cognitive domains tested. Effect sizes for regression analyses are presented as estimated regression coefficients (b) in the results section.

Post-hoc analyses examined how the components of our TES composite score correlated with each other in PLWH with Spearman's rho correlations for continuous variables (trauma, SES, and stress) and Cohen's d for dichotomous variables (food insecurity). We used Bonferroni corrections for multiple comparisons with alpha set at 0.008 (.05/6) for each comparison of two TES components. We used continuous and not dichotomous versions of our trauma, SES, and stress variables in post-hoc analyses to more precisely examine the contribution of each variable by utilizing the full range of variability in each of the scores.

We also examined how the individual components of TES (trauma, economic hardship: food insecurity and SES, and stress) related to the cognitive and functional outcomes in PLWH using Cohen's d for dichotomous variables (food insecurity), Pearson's correlations for

continuous variables approximating a normal distribution (SES, stress), and Spearman's rho

correlations for non-normally distributed continuous variables (trauma). To adjust for multiple

comparisons, alpha was set based on the number of outcomes for each TES component: 0.013

(.05/4).

Results

Study cohort. Participants were mostly men (77.9%), and ranged in age from 35 to 65

years old (M=50.8, SD=8.1). In terms of race and ethnicity, the cohort was 59.0% White, 21.2%

Hispanic or Latino, 15.2% Black or African American, and 4.6% Other. Table 1 provides the

sample demographic, psychiatric, substance use, HIV disease, TES component, cognitive, and

everyday function characteristics by HIV status group. Overall, PLWH had more traumatic

events ($p < .0001$), more food insecurity ($p < .0001$), lower SES ($p < .0001$), and higher

perceived stress ($p < .0001$) compared to individuals without HIV.

………………….…………[INSERT TABLE 1 HERE] ………………………………...…

TES and HIV Status on cognition. We did not find a significant TES*HIV interaction

on global cognition T-scores, but we did find additive main effects of TES ($b = -1.07$; $p = .02$)

and HIV Status ($b = -2.29$; $p = .04$) such that higher TES scores and HIV+ status were related to

worse cognition. When we stratified the groups by HIV status, the TES composite was weakly

and not significantly associated with any of the seven cognitive domains nor global cognition in

the HIV- group. In univariable analyses among PLWH, TES was significantly associated with

worse executive functioning, learning, and working memory (ps $< .007$). With demographic,

educational, psychiatric, and substance use predictors included in the models, TES remained

associated with worse executive functioning ($p =.004$; *coefficient* $= -2.39$), learning ($p = .003$;

coefficient $= -2.40$), and working memory ($p = .006$; *coefficient* $= -2.34$). When current CD4

count was also included in our models, TES remained significantly associated with worse

outcomes in all three domains: executive functioning ($p =.009$; *coefficient* = -2.26), learning (p

= .008; *coefficient* = -2.23), and working memory (p = .005; *coefficient* = -2.53) (Figure 2).

…………………….…………[INSERT FIGURE 2 HERE] …………………………………..….

TES and HIV Status on everyday functioning. We observed a statistically significant

TES*HIV interaction (p = .02) on declines in activities of daily living (ADLs) (Figure 3).

Among HIV- individuals, the TES composite did not relate to ADL declines (p = .76; *coefficient*

= .09). Among PLWH, the TES composite was associated with ADL declines ($p < .0001$;

coefficient = .94) while accounting for demographic, educational, psychiatric, substance use, and

cognitive predictors. When estimated duration of HIV infection was included in our model, TES

remained significantly associated with ADL declines.

…………………….…………[INSERT FIGURE 3 HERE] …………………………………

Post-hoc analyses in PLWH. Among PLWH, correlations between individual

components of TES are shown in Figure 4. The correlation between trauma and stress ($r_s = 0.28$,

$p = 0.002$) was small and significant with a Bonferroni-adjusted significance level of $p=0.008$.

Trauma and SES ($r_s = -0.04$, $p = 0.65$) and SES and stress ($r_s = 0.12$, $p = 0.20$) were not

correlated. Effect sizes for the relationships with the dichotomous food insecurity variable were:

small and non-significant for food insecurity and trauma (Cohen's d = 0.29, $p = 0.15$) and food

insecurity and SES (Cohen's d = -0.40, $p = 0.05$), and medium and significant for food insecurity

and stress (Cohen's d = 0.55, $p = 0.007$).

…………………….…………[INSERT FIGURE 4 HERE] …………………………………

Among PLWH, correlations between individual components of TES and outcomes:

executive function, learning, working memory, and ADL declines are shown in Figure 5. Trauma

had small and non-significant correlations with executive function, learning, and working memory with a Bonferroni-adjusted significance level of $p=.013$. Stress and ADL declines ($r_s = .39$, $p < .0001$) had a medium and significant correlation, while stress had small and non-significant correlations with executive function and working memory. The relationship between food insecurity and ADL declines (Cohen's d $= .52$, $p = .01$) was medium and significant, while food insecurity had small to medium, non-significant relationships with the three cognitive domains. SES had small and non-significant correlations with executive function and working memory.

…………………….…………[INSERT FIGURE 5 HERE] …………………………………

Discussion

In PLWH, elevated composite TES scores related to worse executive function, learning, and working memory performance, as well as worse daily functional abilities. The impact of these common traumatic and stressful experiences in PLWH may help to explain the high rates of mild neurocognitive and functional impairment observed in this population. When individual components of TES were examined, food insecurity and stress were closely related to ADL declines, while TES components had overall small and non-significant relationships with cognitive domains of executive function, learning, and working memory.

While mechanisms underlying the associations among TES and cognitive and everyday functioning are unclear, one possibility for the relation with lower cognitive and everyday functioning among PLWH is the combined effects of multiple adverse experiences and HIV on chronic immune dysregulation and inflammation. Based on our findings, we cannot definitively state that the TES-cognition relationship differs between the HIV+ and HIV- groups because we only observed additive main effects of HIV and TES and not an interaction on global cognition

in our whole sample model. However, our HIV-stratified results suggest an interaction given that we saw a significant relationship between TES and domain-specific cognitive performance in the HIV+ group but not in the HIV- group. A larger sample may clarify whether HIV+ and HIV-groups differ in the association between TES and cognitive function. Given the lower rates of trauma, food insecurity, stress, and less low SES in the HIV- group, we have a limited ability to assess the relation between these adverse experiences and cognitive and functional outcomes in those without HIV. Our findings suggest that TES is especially deleterious for cognitive and everyday functioning among PLWH given that TES remained a significant predictor even when controlling for demographic, educational, substance use, psychiatric, and HIV disease characteristics.

Our post-hoc analyses revealed that, among PLWH, the individual components of our TES composite had small correlations with each other, indicating that trauma, economic hardship, and stress captured distinct but overlapping experiences. Furthermore, our post-hoc analyses showed that the correlations between the individual components of our TES composite and our outcome variables ranged broadly from small to moderate, suggesting that our findings are driven by the combination of these variables acting cumulatively to negatively impact everyday cognition and functional independence.

Our results, which found that elevated TES composite scores are related to difficulties in executive functioning, learning, and working memory, are consistent with previous research that identified executive functioning and learning/memory domains as predominant areas of cognitive deficit in HIV (Heaton et al., 2011). Given these findings, it is possible that trauma, economic hardship, and stress contribute to the worse neurocognitive functioning and the presence of mild neurocognitive impairment in HIV, which is prevalent in about 45% of PLWH. In addition, our

study confirms and extends previous research, which found a relationship between stressful life events and neuropsychological performance in men living with HIV, but not in men without HIV (Pukay-Martin et al., 2003). Not only did we confirm this relationship, but we found that other socioenvironmental factors, such as economic hardship, significantly influence this relationship in a sample of men and women (although predominantly, 84%, men) living with HIV. These findings have clear clinical utility for PLWH's overall healthcare. Specifically, these findings point toward screenings for adverse experiences. These screenings may allow for directed, comprehensive, services and resources, provided with cultural humility, that address social and structural factors. Such screenings and services may help to break the cycle of exposure to chronically stressful and traumatic contexts that may play a role in cognitive and functional impairment. Adversity assessments may also help to identify those who require additional screening for HIV-associated cognitive impairment.

Our sample of participants without HIV reported a limited amount of trauma, economic hardship, and stress, which contributed to a restricted TES composite range. This restricted range may have contributed to the lack of relationship observed between our predictors and outcomes in this group. Thus, we have limited evidence to claim that trauma, economic hardship, and stress are unrelated to cognition and everyday functioning in individuals without HIV.

There were a number of strengths in our study. First, we were able to identify significant effects of trauma, economic hardship, and stress on three cognitive domains and everyday functioning in a medium-sized sample of PLWH and compare these effects to those seen in a HIV- group. Second, our study utilized a comprehensive neuropsychological battery to assess cognitive functioning, which used multiple tests to tap seven domains of cognition. Finally, our study controlled for many more traditional predictors of cognitive and functional outcomes in

PLWH than previous studies. Even when controlling for these covariates, results remained significant, demonstrating a unique and important contribution of adversity to these outcomes in PLWH.

Our study also had several limitations. By nature, the cross-sectional design precludes detection of casual inference from the observed relationship of trauma, economic hardship, and stress with neurocognitive and everyday functioning in HIV. We also cannot rule out the possibility of causality in the opposite direction, such that worse neurocognitive and everyday function contribute to risk for trauma, economic hardship, and stress. Longitudinal studies, which are planned, are necessary to expand our understanding and explore the direction of effects between these factors. Our measures of trauma, stress, and economic hardship, were temporally limited to assessment of recent traumatic events (past year), recent perceived stress (past month), SES (years of education, current or longest held occupation, and current total household income), and food insecurity (current), and did not capture cumulative stressors over the lifetime. With these time-frame constraints, our study lacked indicators of early life stress such as childhood trauma, which has been shown to have an interactive effect with HIV on neuropsychological functioning and structural morphology of the brain (Clark et al., 2012; Spies, Ahmed-Leitao, Fennema-Notestine, Cherner, & Seedat, 2016). Our trauma scale consisted of five items from the WHI Life Events Scale and has not been psychometrically validated as a measure of traumatic events. To better capture trauma, the 10-item Brief Trauma Questionnaire (Schnurr, Vielhauer, Weathers, & Findler, 1999), which assesses type and severity of traumatic event and the 20-item PTSD Checklist for DSM-5 (Blevins, Weathers, Davis, Witte, & Domino, 2015), which captures severity of PTSD symptoms, should be employed in future studies. Moreover, our study did not assess experiences of stigma and discrimination, a form of adversity that can act as a

psychosocial stressor (Williams, 1999). Many PLWH experience discrimination due to their HIV or AIDS status, and/or the intersection of other identities such as sexual orientation, race/ethnicity, gender identity, and/or socioeconomic position, and these common experiences relate to worse health outcomes (Bird, Bogart, & Delahanty, 2004; Logie & Gadalla, 2009; Parker & Aggleton, 2003; Valdiserri, 2002)

To the best of our knowledge this is the first study to examine the combined relationship of adverse social, structural, and psychological factors such as trauma, economic hardship, and stress concurrently with HIV on neurocognitive and everyday functioning outcomes. Given that there are high rates of sexual and physical abuse, trauma, and poverty among those living with HIV, the impact of these acute and chronic experiences should be a research priority with high clinical relevance, particularly in a population that often experiences compromised neurocognitive and immunological functioning. Clinically, assessing and addressing traumatic, stressful, and other adverse events in holistic and culturally-informed ways should be a part of standard HIV care. Future research should investigate the impact of trauma, economic hardship, and stress on the confluence of inflammation, immune dysregulation, and associated neural alterations (functional, structural, metabolic, and connective) in PLWH. In particular, examination of biomarkers of stress and trauma in PLWH may help to understand mechanisms underlying the associations between TES and neurocognitive and everyday function observed in this study. Efforts to reduce trauma, poverty, and other stressful contexts and developing resources to help people manage and cope with past and current adverse circumstances could be relevant to decreasing neurocognitive impairment, particularly the high rates of mild neurocognitive disorder, in PLWH.

Acknowledgements

Disclosures: No conflicts of interest were declared.

Table 1. *Sample characteristics* (*n* = 217)

	HIV- (*n* = 95)	HIV+ (*n* = 122)	*p* value[a]
Demographic			
Age, *M (SD)*	51.1 (7.7)	50.5 (8.5)	.611
Gender (% men)	70.5%	83.6%	.022
Race/ethnicity (%)			.052
Black or African American	13.7%	16.4%	
Hispanic or Latino	19.0%	23.0%	
White	66.3%	53.3%	
Other	1.1%	7.4%	
Education (years), *M (SD)*	15.0 (2.3)	14.0 (2.4)	.002
Psychiatric			
Lifetime MDD (%)	20.4%	53.4%	<.0001
Substance Use			
Current Any Substance Use Disorder	1.08%	3.36%	.256
Lifetime Any Substance Disorder (except Alcohol and Cannabis) (%)	19.4%	50.8%	<.0001
Lifetime Alcohol Use Disorder (%)	30.1%	51.7%	.002
Lifetime Cannabis Use Disorder (%)	17.2%	28.3%	.055
HIV Disease Characteristics			
AIDS (%)	-	60.7%	-
Duration of infection (years), *M (SD)*	-	17.1 (8.7)	-
Nadir CD4, *Median (IQR)*	-	180 (47, 329)	-
Current CD4, *Median (IQR)*	-	633 (425, 851)	-
On cART (%)	-	95.8%	-
Detectable viral load in plasma (%)	-	6.6%	-
TES Composite Components			
Traumatic Events	.9 (1.2)	.3 (.6)	<.0001
Food Insecurity	6.5%	30.8%	<.0001
SES (Hollingshead index)	49.3 (9.0)	38.3 (11.9)	<.0001
Perceived stress (PSS-10)	10.4 (6.4)	15.2 (8.3)	<.0001
Cognitive and Functional Outcomes			
Global cognitive impairment (%)	27.4%	39.3%	.063
Global Mean T-score, *M (SD)*	49.8 (6.0)	46.9 (6.9)	.0013
Executive Function Mean T-score, *M (SD)*	52.8 (9.4)	48.0 (9.6)	.0003
Learning Mean T-score, *M (SD)*	44.7 (9.3)	41.1 (8.9)	.004
Recall Mean T-score, *M (SD)*	44.2 (9.2)	41.6 (9.2)	.045
Working Memory Mean T-score, *M (SD)*	49.4 (10.7)	48.2 (9.1)	.386
Verbal Mean T-score, *M (SD)*	50.6 (6.7)	49.4 (8.4)	.267
Speed of Processing Mean T-score, *M (SD)*	52.1 (8.4)	49.0 (8.5)	.007
Motor Mean T-score, *M (SD)*	53.5 (10.5)	50.0 (10.4)	.015
ADL declines, *M (SD)*	.5 (1.2)	2.1 (3.0)	<.0001

[a]Based on independent sample t-tests and Chi-Square tests
Note. MDD = Major Depressive Disorder; cART = combination antiretroviral therapy; SES=Socioeconomic Status
Note. Current MDD not included in tables or analyses because prevalence was low (Current MDD: 0% for HIV-)

Figure 1. Distribution of TES composite by HIV status group
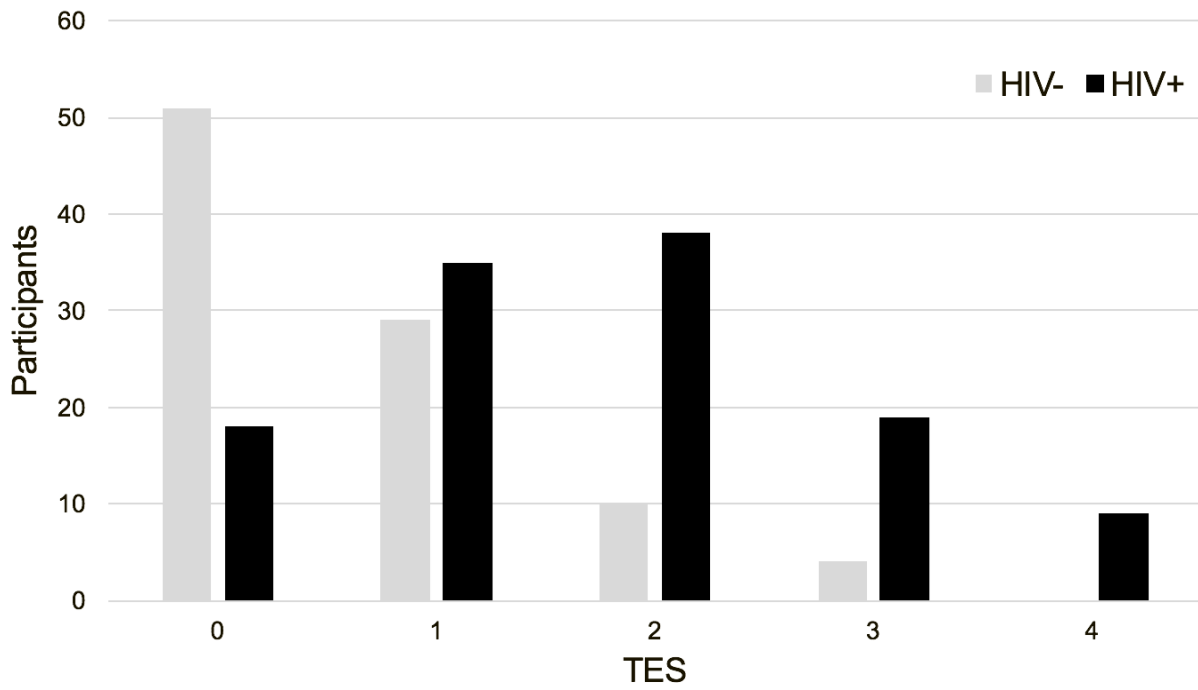
Note: TES = Trauma, economic hardship, and stress

Figure 2. PLWH with higher TES had significantly lower executive function, learning, and working memory performance
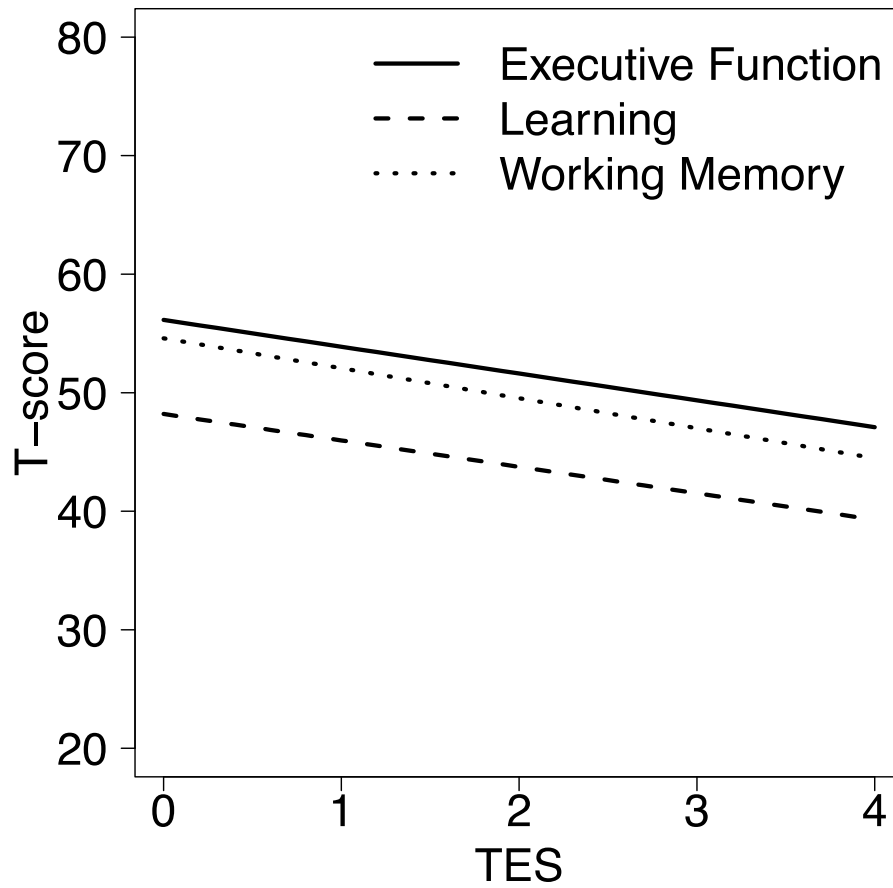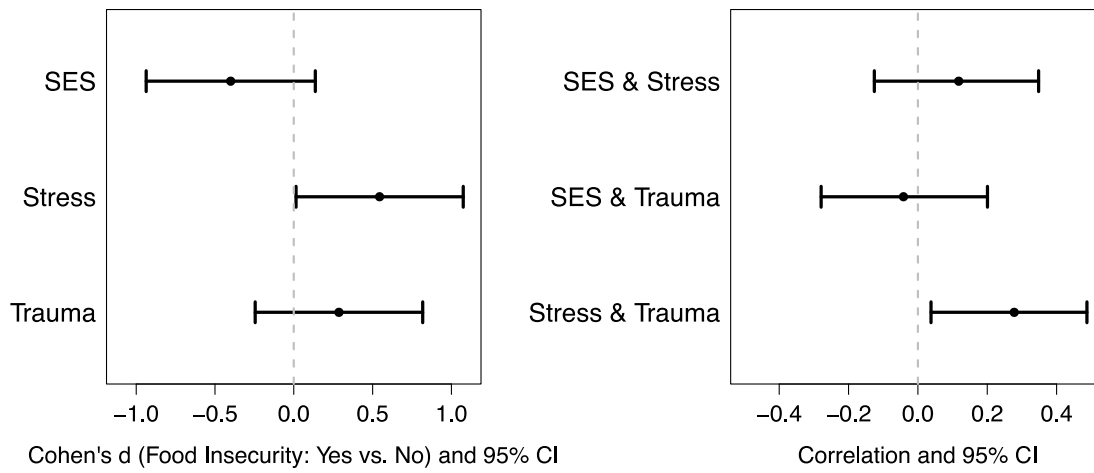

Note: PLWH = People living with HIV; TES = Trauma, economic hardship, and stress

Figure 3. PLWH with higher TES scores had significantly more declines in activities of daily living compared to individuals without HIV
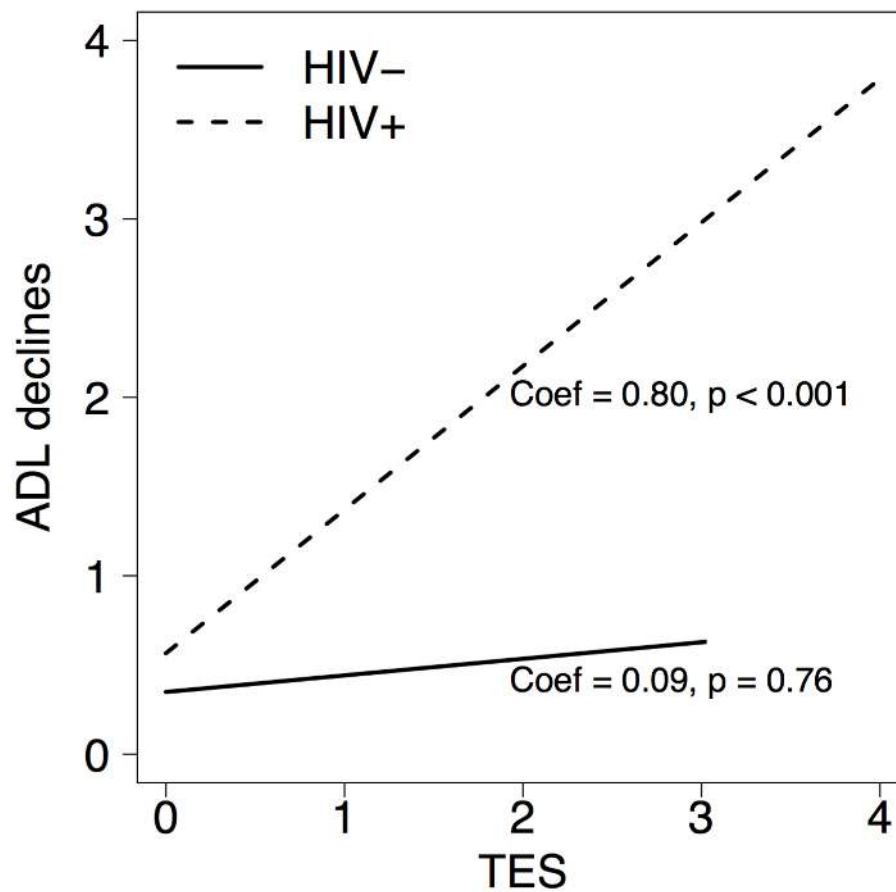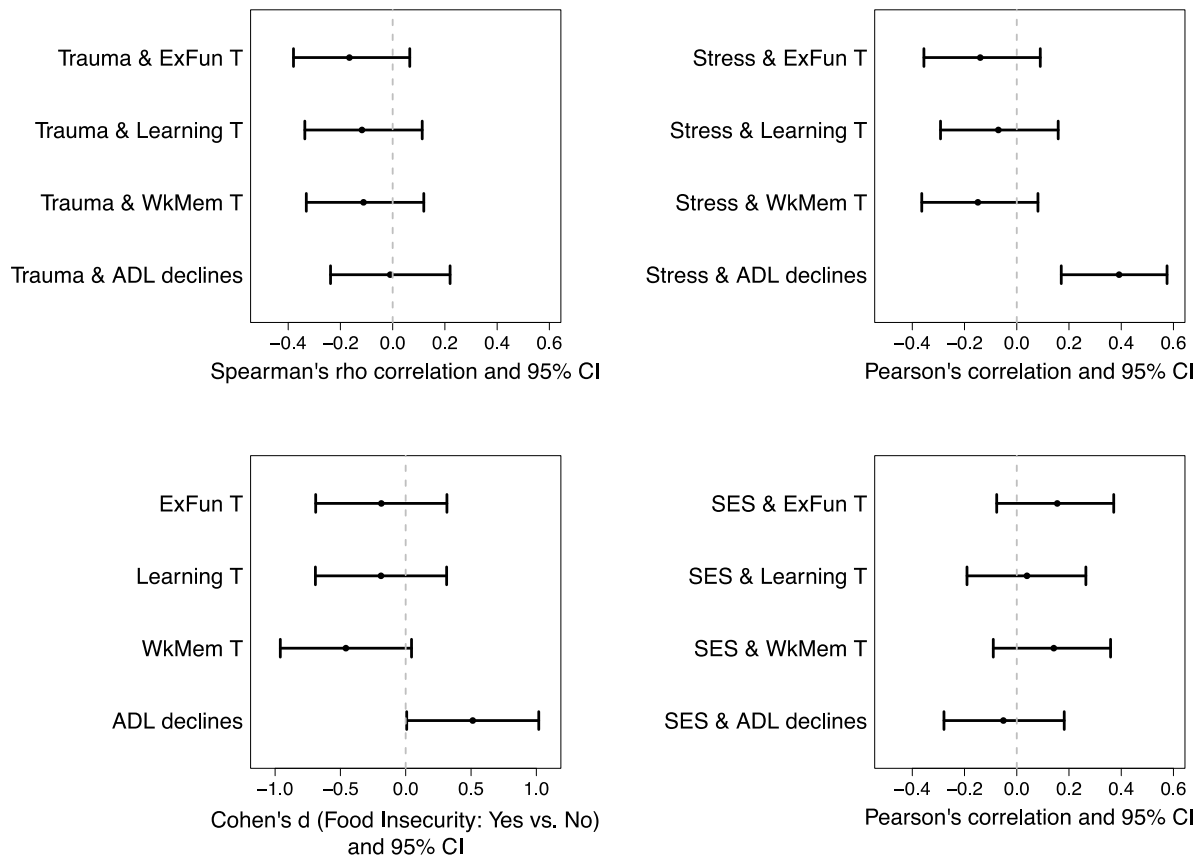

Note: PLWH = People living with HIV; TES = Trauma, economic hardship, stress; ADL = Activities of Daily Living

Figure 4. Correlations of four TES components with each other in PLWH

Note: PLWH = People living with HIV; TES = Trauma, economic hardship, stress; SES = Socioeconomic status

Figure 5. Correlations of four TES components with cognitive and everyday functioning outcomes in PLWH

Note: PLWH = People living with HIV; TES = Trauma, economic hardship, stress; ExFun = Executive Function; WkMem = Working Memory; ADL = Activities of Daily Living; SES = Socioeconomic status

References

Bird, S. T., Bogart, L. M., & Delahanty, D. L. (2004). Health-related correlates of perceived discrimination in HIV care. *AIDS Patient Care STDS, 18*(1), 19-26. doi: 10.1089/108729104322740884

Blevins, C. A., Weathers, F. W., Davis, M. T., Witte, T. K., & Domino, J. L. (2015). The posttraumatic stress disorder checklist for DSM-5 (PCL-5): Development and initial psychometric evaluation. *Journal of Traumatic Stress, 28*(6), 489-498. doi: 10.1002/jts.22059

Brew, B., Sidtis, J., Petito, C., & Price, R. (1988). The neurologic complications of AIDS and human immunodeficiency virus infection. *Advances in Contemporary Neurology. Edited by Plum F. Philadelphia, PA, FA Davis*, 1-49.

Brief, D. J., Bollinger, A., Vielhauer, M., Berger-Greenstein, J., Morgan, E., Brady, S., . . . Group, C. S. (2004). Understanding the interface of HIV, trauma, post-traumatic stress disorder, and substance use and its implications for health outcomes. *AIDS Care, 16*(sup1), 97-120. doi: 10.1080/09540120412301315259

Castelo, J. M. B., Sherman, S. J., Courtney, M. G., Melrose, R. J., & Stern, C. E. (2006). Altered hippocampal-prefrontal activation in HIV patients during episodic memory encoding. *Neurology, 66*(11), 1688-1695. doi: 10.1212/01.wnl.0000218305.09183.70

Clark, U. S., Cohen, R. A., Sweet, L. H., Gongvatana, A., Devlin, K. N., Hana, G. N., . . . White, T. L. (2012). Effects of HIV and early life stress on amygdala morphometry and neurocognitive function. *Journal of the International Neuropsychological Society, 18*(4), 657-668. doi: 10.1017/S1355617712000434

Cohen, S., Kamarck, T., & Mermelstein, R. (1983). A global measure of perceived stress. *Journal of health and social behavior*, 385-396.

Cohen, S., & Williamson, G. (1988). Perceived stress in a probability sample of the United States. In S. Spacapan & S. Oskamp (Eds.), *The social psychology of health*. Newbury Park, CA: Sage.

Cysique, L. A., Franklin Jr, D., Abramson, I., Ellis, R. J., Letendre, S., Collier, A., . . . Morgello, S. (2011). Normative data and validation of a regression based summary score for assessing meaningful neuropsychological change. *J Clin Exp Neuropsychol, 33*(5), 505-522. doi: 10.1080/13803395.2010.535504

De Kloet, E. R., Joëls, M., & Holsboer, F. (2005). Stress and the brain: from adaptation to disease. *Nature reviews. Neuroscience, 6*(6), 463. doi: 10.1038/nrn1683

Dinkel, K., Ogle, W. O., & Sapolsky, R. M. (2002). Glucocorticoids and central nervous system inflammation. *J Neurovirol, 8*(6), 513-528. doi: 10.1080/13550280290100914

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., . . . Atkinson, J. H. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy CHARTER Study. *Neurology, 75*(23), 2087-2096. doi: 10.1212/ WNL.0b013e318200d727

Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., Leblanc, S., . . . Group, H. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol, 17*(1), 3-16. doi: 10.1007/s13365-010-0006-1

Heaton, R. K., Marcotte, T. D., Mindt, M. R., Sadek, J., Moore, D. J., Bentley, H., . . . GROUP, H. (2004). The impact of HIV-associated neuropsychological impairment on everyday

functioning. *Journal of the International Neuropsychological Society, 10*(3), 317-331. doi: 10.10170S1355617704102130

Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., & Stefaniak, M. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *Aids, 18*(Suppl 1), S19-S25.

Hollingshead, A. B. (1975). Four factor index of social status. *Unpublished Manuscript, Yale University, New Haven, CT*.

Kessler, R. C., McLaughlin, K. A., Green, J. G., Gruber, M. J., Sampson, N. A., Zaslavsky, A. M., . . . Angermeyer, M. (2010). Childhood adversities and adult psychopathology in the WHO World Mental Health Surveys. *The British Journal of Psychiatry, 197*(5), 378-385. doi: 10.1192/bjp.bp.110.080499

Lawton, M. P., & Brody, E. (1969). Assessment of older people: Self-maintaining and instrumental activities of daily living. *Gerontologist, 9*(3), 179-186.

Logie, C., & Gadalla, T. M. (2009). Meta-analysis of health and demographic correlates of stigma towards people living with HIV. *AIDS Care, 21*(6), 742-753. doi: 10.1080/09540120802511877

Lupien, S., Gaudreau, S., Tchiteya, B., Maheu, F., Sharma, S., Nair, N., . . . Meaney, M. (1997). Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. *The Journal of Clinical Endocrinology & Metabolism, 82*(7), 2070-2075. doi: 10.1210/jcem.82.7.4075

Lupien, S. J., McEwen, B. S., Gunnar, M. R., & Heim, C. (2009). Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nature reviews. Neuroscience, 10*(6), 434–445. doi: 10.1038/nrn2639

Machtinger, E., Wilson, T., Haberer, J. E., & Weiss, D. (2012). Psychological trauma and PTSD in HIV-positive women: a meta-analysis. *AIDS and Behavior, 16*(8), 2091-2100. doi: 10.1007/s10461-011-0127-4

Maki, P. M., Cohen, M. H., Weber, K., Little, D. M., Fornelli, D., Rubin, L. H., . . . Martin, E. (2009). Impairments in memory and hippocampal function in HIV-positive vs HIV-negative women a preliminary study. *Neurology, 72*(19), 1661-1668. doi: 10.1212/WNL. 0b013e3181a55f65

Marcotte, T. D., Heaton, R. K., Wolfson, T., Taylor, M. J., Alhassoon, O., Arfaa, K., . . . GROUP, H. (1999). The impact of HIV-related neuropsychological dysfunction on driving behavior. *Journal of the International Neuropsychological Society, 5*(7), 579-592.

Martinez, D. A., Goggin, K., Catley, D., Gerkovich, M. M., Williams, K., Wright, J., & Berkley-Patton, J. (2012). Do coping styles mediate the relationship between substance use and educational attainment and antiretroviral adherence? *AIDS and Behavior, 16*(8), 2319-2329. doi: 10.1007/s10461-012-0222-1

Massad, L. S., Agniel, D., Minkoff, H., Watts, D. H., D'Souza, G., Levine, A. M., . . . Weber, K. (2011). Impact of stress and depression on the frequency of squamous intraepithelial lesions. *Journal of lower genital tract disease, 15*(1), 42-47. doi: 10.1097/LGT.0b013e3181e66a82

McArthur, J. C. (1994). Neurological and Neuropathological Manifestations of HIV Infection. In Grant I. & M. A. (Eds.), *Neuropsychology of HIV infection* (pp. 56-107). New York: Oxford University Press.

McEwen, B. S. (2000). Effects of adverse experiences for brain structure and function. *Biological psychiatry, 48*(8), 721-731. doi: 10.1016/S0006-3223(00)00964-1

Michael, Y. L., Carlson, N. E., Chlebowski, R. T., Aickin, M., Weihs, K. L., Ockene, J. K., . . . Ritenbaugh, C. (2009). Influence of stressors on breast cancer incidence in the Women's Health Initiative. *Health psychology : official journal of the Division of Health Psychology, American Psychological Association*, *28*(2), 137-146. doi: 10.1037/a0012982

Moore, R. C., Paolillo, E. W., Heaton, A., Fazeli, P. L., Jeste, D. V., & Moore, D. J. (2017). Clinical utility of the UCSD Performance-Based Skills Assessment—Brief (UPSA-B) in adults living with HIV: Associations with neuropsychological impairment and patient-reported everyday functioning difficulties. *PLoS One*, *12*(8), e0183614. doi: 10.1371/journal.pone.0183614

Morgan, E. E., Woods, S. P., & Grant, I. (2012). Intra-individual Neurocognitive Variability Confers Risk of Dependence in Activities of Daily Living among HIV-Seropositive Individuals without HIV-Associated Neurocognitive Disorders. *Archives of Clinical Neuropsychology*, *27*(3), 293-303. doi: 10.1093/arclin/acs003

Office of Management and Budget. (1997). Revisions to the standards for the classification of federal data on race and ethnicity. https://www.whitehouse.gov/omb/fedreg_1997standards

Parker, R., & Aggleton, P. (2003). HIV and AIDS-related stigma and discrimination: a conceptual framework and implications for action. *Social Science & Medicine*, *57*(1), 13-24. doi: 10.1016/S0277-9536(02)00304-0

Pence, B. W., Reif, S., Whetten, K., Leserman, J., Stangl, D., Swartz, M., . . . Mugavero, M. J. (2007). Minorities, the poor, and survivors of abuse: HIV-infected patients in the US deep South. *Southern medical journal*, *100*(11), 1114-1122. doi: 10.1097/01.smj.0000286756.54607.9f

Pukay-Martin, N. D., Cristiani, S. A., Saveanu, R., & Bornstein, R. A. (2003). The relationship between stressful life events and cognitive function in HIV-infected men. *The Journal of neuropsychiatry and clinical neurosciences*, *15*(4), 436-441.

Rabkin, J. G., McElhiney, M., Ferrando, S. J., Van Gorp, W., & Lin, S. H. (2004). Predictors of employment of men with HIV/AIDS: a longitudinal study. *Psychosomatic medicine*, *66*(1), 72-78. doi: 10.1097/01.PSY.0000108083.43147.6D

Radley, J., Morilak, D., Viau, V., & Campeau, S. (2015). Chronic stress and brain plasticity: mechanisms underlying adaptive and maladaptive changes and implications for stress-related CNS disorders. *Neuroscience and biobehavioral reviews*, *58*, 79-91. doi: 10.1016/j.neubiorev.2015.06.018

Ruberman, W., Weinblatt, E., Goldberg, J. D., & Chaudhary, B. S. (1984). Psychosocial influences on mortality after myocardial infarction. *New England Journal of Medicine*, *311*(9), 552-559. doi: 10.1056/NEJM198408303110902

Rubin, L. H., Cook, J. A., Weber, K. M., Cohen, M. H., Martin, E., Valcour, V., . . . Alden, C. (2015). The association of perceived stress and verbal memory is greater in HIV-infected versus HIV-uninfected women. *J Neurovirol*, *21*(4), 422-432. doi: 10.1007/s13365-015-0331-5

Rubin, L. H., Meyer, V. J., Jamadar, R., Sundermann, E. E., Wu, M., Weber, K. M., . . . Maki, P. M. (2016a). Prefrontal cortical volume loss is associated with stress-related deficits in verbal learning and memory in HIV-infected women. *Neurobiology of disease*, *92*(Pt B), 166-174. doi: 10.1016/j.nbd.2015.09.010

Rubin, L. H., Wu, M., Sundermann, E. E., Meyer, V. J., Smith, R., Weber, K. M., . . . Maki, P. M. (2016b). Elevated stress is associated with prefrontal cortex dysfunction during a verbal memory task in women with HIV. *J Neurovirol, 22*(6), 840-851. doi: 10.1007/s13365-016-0446-3

Samji, H., Cescon, A., Hogg, R. S., Modur, S. P., Althoff, K. N., Buchacz, K., . . . Gill, M. J. (2013). Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One, 8*(12), e81355. doi: 10.1371/journal.pone.0081355

Schnurr, P., Vielhauer, M., Weathers, F., & Findler, M. (1999). The brief trauma questionnaire. *National Center for PTSD*. White River Junction, VT.

Scott, K. M., McLaughlin, K. A., Smith, D. A., & Ellis, P. M. (2012). Childhood maltreatment and DSM-IV adult mental disorders: comparison of prospective and retrospective findings. *The British Journal of Psychiatry, 200*(6), 469-475. doi: 10.1192/bjp.bp.111.103267

Sorrells, S. F., Caso, J. R., Munhoz, C. D., & Sapolsky, R. M. (2009). The stressed CNS: when glucocorticoids aggravate inflammation. *Neuron, 64*(1), 33-39. doi: 10.1016/j.neuron.2009.09.032

Spies, G., Afifi, T. O., Archibald, S. L., Fennema-Notestine, C., Sareen, J., & Seedat, S. (2012). Mental health outcomes in HIV and childhood maltreatment: a systematic review. *Systematic reviews, 1*(1), 30. doi: 10.1186/2046-4053-1-30

Spies, G., Ahmed-Leitao, F., Fennema-Notestine, C., Cherner, M., & Seedat, S. (2016). Effects of HIV and childhood trauma on brain morphometry and neurocognitive function. *J Neurovirol, 22*(2), 149-158. doi: 10.1007/s13365-015-0379-2

Thames, A. D., Kuhn, T. P., Mahmood, Z., Bilder, R. M., Williamson, T. J., Singer, E. J., & Arentoft, A. (2017). Effects of social adversity and HIV on subcortical shape and neurocognitive function. *Brain Imaging and Behavior*, 1-13. doi: 10.1007/s11682-017-9676-0

Troxel, W. M., Matthews, K. A., Bromberger, J. T., & Sutton-Tyrrell, K. (2003). Chronic stress burden, discrimination, and subclinical carotid artery disease in African American and Caucasian women. *Health Psychology, 22*(3), 300. doi: 10.1037/0278-6133.22.3.300

Valdez, A. N., Rubin, L. H., & Neigh, G. N. (2016). Untangling the Gordian knot of HIV, stress, and cognitive impairment. *Neurobiology of stress, 4*, 44-54. doi: 10.1016/j.ynstr.2016.02.005

Valdiserri, R. O. (2002). HIV/AIDS stigma: An impediment to public health. *American Journal of Public Health, 92*(3), 341-342.

van Gorp, W. G., Baerwald, J. P., Ferrando, S. J., McElhiney, M. C., & Rabkin, J. G. (1999). The relationship between employment and neuropsychological impairment in HIV infection. *Journal of the International Neuropsychological Society, 5*(6), 534-539.

Vivithanaporn, P., Heo, G., Gamble, J., Krentz, H., Hoke, A., Gill, M., & Power, C. (2010). Neurologic disease burden in treated HIV/AIDS predicts survival A population-based study. *Neurology, 75*(13), 1150-1158. doi: 10.1212/WNL.0b013e3181f4d5bb

Whetten, K., Leserman, J., Lowe, K., Stangl, D., Thielman, N., Swartz, M., . . . Van Scoyoc, L. (2006). Prevalence of childhood sexual abuse and physical trauma in an HIV-positive sample from the deep south. *American Journal of Public Health, 96*(6), 1028-1030. doi: 10.2105/AJPH.2005.063263

Wilding, J., Andrews, B., & Hejdenberg, J. (2007). Relations between life difficulties, measures of working memory operation, and examination performance in a student sample. *Memory, 15*(1), 57-62. doi: 10.1080/09658210601106447

Williams, D. R. (1999). Race, socioeconomic status, and health the added effects of racism and discrimination. *Annals of the New York Academy of Sciences, 896*(1), 173-188. doi: 10.1111/j.1749-6632.1999.tb08114.x

Williamson, T. J., Mahmood, Z., Kuhn, T. P., & Thames, A. D. (2017). Differential relationships between social adversity and depressive symptoms by HIV status and racial/ethnic identity. *Health Psychology, 36*(2), 133-142. doi: 10.1037/hea0000458

Wittchen, H.-U., Robins, L. N., Cottler, L. B., Sartorius, N., Burke, J. D., & Regier, D. (1991). Cross-cultural feasibility, reliability and sources of variance of the Composite International Diagnostic Interview (CIDI). The Multicentre WHO/ADAMHA Field Trials. *The British Journal of Psychiatry, 159*(5), 645-653.