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Effects of HIV and Early Life Stress on Amygdala Morphometry and Neurocognitive Function

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Abstract

Both HIV infection and high levels of early life stress (ELS) have been related to abnormalities in frontal-subcortical structures, yet the combined effects of HIV and ELS on brain structure and function have not been previously investigated. In this study we assessed 49 non-demented HIV-seropositive (HIV+) and 47 age-matched HIV-seronegative healthy control (HC) adults. Levels of ELS exposure were quantified and used to define four HIV-ELS groups: HC Low-ELS ($N = 20$); HC High-ELS ($N = 27$); HIV+ Low-ELS ($N = 24$); HIV+ High-ELS ($N = 25$). An automated segmentation tool measured volumes of brain structures known to show HIV-related or ELS-related effects; a brief neurocognitive battery was administered. A significant HIV-ELS interaction was observed for amygdala volumes, which was driven by enlargements in HIV+ High-ELS participants. The HIV+ High-ELS group also demonstrated significant reductions in psychomotor/processing speed compared with HC Low-ELS. Regression analyses in the HIV+ group revealed that amygdala enlargements were associated with higher ELS, lower nadir CD4 counts, and reduced psychomotor/processing speed. Our results suggest that HIV infection and high ELS interact to increase amygdala volume, which is associated with neurocognitive dysfunction in HIV+ patients. These findings highlight the lasting neuropathological influence of ELS and suggest that high ELS may be a significant risk factor for neurocognitive impairment in HIV-infected individuals. (*JINS*, 2012, *18*, 657–668)

Keywords: HIV, Stress, Amygdala, Neuroimaging, Cognition

INTRODUCTION

HIV infection can have significant neuropathological consequences (e.g., Jernigan et al., 2011). Several brain regions, including the basal ganglia, subcortical regions, and frontal cortices, are known to be particularly susceptible to HIV (Wiley et al., 1999). Consistent with these findings, neuroimaging studies have commonly revealed volumetric, functional, and metabolic abnormalities within frontal-subcortical regions (Ances et al., 2006; Aylward et al., 1993; Becker et al., 2011; Cohen, Harezlak, Gongvatana, et al., 2010; Jernigan et al., 1993; Paul, Cohen, Navia, & Tashima, 2002; Towgood et al., 2012), which have in turn been linked to increased neurocognitive difficulty in HIV+ patients (Castelo, Sherman, Courtney, Melrose, & Stern, 2006; Cohen, Harezlak, Schifitto, et al., 2010; Harezlak et al., 2011; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008; Moore et al., 2006; Paul, Ernst, et al., 2008).

HIV-associated neurocognitive disorders (HAND) represent a significant public health challenge. Up to 50% of individuals with HIV develop some form of cognitive impairment during the course of their disease (Heaton et al., 2010, 2011), suggesting that some patients might be at greater risk for developing neurocognitive impairment than others. In an era in which HIV-infected individuals are surviving into old age due to advances in combination

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antiretroviral therapies (cART), it is vital that we understand the various etiological factors associated with HAND to better prevent and treat these disorders (Clark & Cohen, 2010). Several factors have been associated with increased risk for neurocognitive impairment in HIV+ patients, including comorbid medical conditions [e.g., hepatitis C virus (HCV) (Clifford, Evans, Yang, & Gulick, 2005; Devlin et al., 2012; Martin-Thormeyer & Paul, 2009)] and psychosocial comorbidities [e.g., alcoholism (Fama, Rosenbloom, Nichols, Pfefferbaum, & Sullivan, 2009; Schulte, Mueller-Oehring, Rosenbloom, Pfefferbaum, & Sullivan, 2005), drug abuse (Rippeth et al., 2004)].

Early life stress (ELS) is a potentially important psychosocial factor that is likely associated with increased risk of HAND, yet it has received little attention with respect to HIV comorbidity. The HIV epidemic in the United States occurs largely within a context of considerable social inequality (Adimora et al., 2006; CDC, 2005; DHHS, 2001; Eaton & Muntaner, 1999; Hader, Smith, Moore, & Holmberg, 2001; Krueger, Wood, Diehr, & Maxwell, 1990; St Louis et al., 1991; Wenzel & Tucker, 2005). Consequently, substantial numbers of HIV-infected individuals are exposed to environmental conditions associated with high levels of ELS. There is strong evidence that significant exposure to ELS can have pathological effects on the brain (Andersen et al., 2008; Cohen, Grieve, et al., 2006; Mehta et al., 2009; Paul, Henry, et al., 2008; Seckfort et al., 2008; Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Tottenham et al., 2009). It is, therefore, critical for neuroAIDS research to develop a better understanding of how ELS affects neuropathology in HIV+ patients, as it is possible that some of the observed HIV-related neural abnormalities may be partially attributable to, or even compounded by, the neuropathological effects associated with experiencing high levels of ELS.

Exposure to substantial amounts of ELS in otherwise healthy individuals has been associated with structural abnormalities in frontal-subcortical regions, including decreased anterior cingulate cortex (ACC) (Cohen, Grieve, et al., 2006), caudate (Cohen, Grieve, et al., 2006), and hippocampal (Andersen et al., 2008; Stein et al., 1997) volumes, as well as increased amygdala volumes (Mehta et al., 2009; Tottenham et al., 2009). There is thus significant overlap between the neuropathology of HIV and ELS, with both involving similar structures in frontal-subcortical networks. Yet, to our knowledge no study has examined the brain effects of ELS in HIV-infected individuals. In the current study we investigated whether high levels of ELS modulate HIV-related structural brain abnormalities and neurocognitive impairment. We examined the effects of HIV-serostatus and ELS exposure on brain structure and neurocognitive function in HIV-seropositive and HIV-seronegative individuals. Volumes of brain regions known to show HIV-related or ELS-related effects [i.e., caudate (Ances et al., 2006; Becker et al., 2011; Cohen, Grieve, et al., 2006; Cohen, Harezlak, Schifitto, et al., 2010), putamen (Becker et al., 2011), hippocampus (Andersen et al., 2008; Stein et al., 1997), ACC (Cohen, Grieve, et al., 2006), amygdala (Mehta et al., 2009; Tottenham et al., 2009)] were measured using magnetic resonance imaging (MRI). We administered a battery of neurocognitive measures and assessed the relation between brain structure and neurocognitive performance.

We predicted that the HIV+ group would demonstrate volumetric abnormalities in the caudate, putamen, and hippocampus (Becker et al., 2011; Cohen, Harezlak, Schifitto, et al., 2010; Hall et al., 1996; Jernigan et al., 1993; Paul, Ernst, et al., 2008; Petito, Roberts, Cantando, Rabinstein, & Duncan, 2001; Sa et al., 2004), and that individuals with high ELS exposure would display volumetric abnormalities in the ACC, caudate, hippocampus, and amygdala. We further predicted that HIV+ patients with high ELS would display the greatest volumetric effects. Lastly, we expected that both degree of ELS exposure (Tottenham et al., 2009) and markers of HIV-disease severity (e.g., nadir CD4 lymphocyte count) would correlate with degree of structural abnormality, and that greater volumetric abnormality would be associated with greater cognitive impairment in HIV-infected individuals (Cardenas et al., 2009; Childs et al., 1999; Cohen, Harezlak, Schifitto, et al., 2010; Jernigan et al., 2011; Valcour et al., 2006).

METHOD

Participants

We included 49 non-demented HIV-seropositive participants (HIV+) and 47 HIV-seronegative healthy control participants (HC). HIV+ participants were recruited from The Miriam Hospital Immunology Clinic. HC participants were acquaintances of HIV+ participants and individuals recruited from the community. All scored above 23 on the Mini-Mental State Exam (MMSE) (Folstein, Folstein, & McHugh, 1975) and were fluent in English. We excluded participation on the basis of reported history of developmental or learning disability; major psychiatric illness (e.g., schizophrenia, bipolar disorder); positive urine toxicology (cocaine, methamphetamine, opiates); neurological illness affecting the central nervous system; and traumatic head injury with a loss of consciousness of 10 + min. Substance use exclusion criteria were current alcohol dependence; use of heroin/opiates/intravenous drugs within the past 12 months; and use of cocaine within the past 3 months. This research was approved by The Miriam Hospital's Institutional Review Board. All individuals gave their informed consent and were financially compensated for their time.

Demographic Measures

Disease duration in HIV+ participants was obtained by self-report and verified against the medical record. History of cART use, nadir CD4 levels (i.e., the lowest ever CD4 count), current CD4 levels, and viral load (i.e., plasma HIV RNA levels) were obtained from the medical record. Forty-one of 49 HIV+ participants were on cART. Nadir CD4 levels ranged from 0 to 845 cells/μL. Current CD4 levels ranged from 105 to 1491 cells/μL. HIV+ participants were categorized in terms of viral load as undetectable (<75 copies/mL) or

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detectable ($\geq$75 copies/mL); these data were unavailable for two participants. All HIV+ and HC participants were assessed for active HCV infection, defined as positive HCV antibody, determined by ELISA, and positive qualitative HCV RNA measured by PCR.

The Wechsler Test of Adult Reading (WTAR) estimated premorbid levels of intellectual function (Wechsler, 2001); scaled scores were derived using published normative data. The Kreek-McHugh-Schluger-Kellogg scale (KMSK) assessed history of alcohol and drug use, and provided three subscales that characterized lifetime consumption of alcohol (KMSK-A), cocaine (KMSK-C), and opiates (KMSK-O) (Kellogg et al., 2003). The Center for Epidemiological Studies-Depression Scale (CESD) (Radloff, 1977), Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983), and Posttraumatic Stress Disorder Checklist—Civilian (PCLC) (Weathers, Litz, Herman, Huska, & Keane, 1993) evaluated current levels of depression, stress, and posttraumatic stress disorder (PTSD) symptoms, respectively.

Early Life Stress Quantification

Participants completed the Early Life Stress Questionnaire (ELSQ) (Cohen, Paul, et al., 2006), which assessed the occurrence of 17 adverse life-events (e.g., family conflict, abuse, bullying, neglect) before age 18 years. The ELSQ has been used in several studies examining consequences of ELS exposure (Cohen, Grieve, et al., 2006; Cohen, Paul, et al., 2006; Paul, Henry, et al., 2008; Seckfort et al., 2008). This scale was selected based on its documented sensitivity in detecting neural abnormalities in relation to ELS history in adults (Cohen, Grieve, et al., 2006; Paul, Henry, et al., 2008; Seckfort et al., 2008).

HIV+ and HC groups were divided into High-ELS and Low-ELS exposure groups based on their ELSQ responses. A cut-point of $\geq$3 adverse events has been shown to provide the greatest discrimination on the basis of ELS for both behavioral and neural measures (Cohen, Grieve, et al., 2006; Cohen, Paul, et al., 2006; Seckfort et al., 2008). High-ELS was thus defined as endorsement of 3 or more ELS events, and Low-ELS was classified as endorsement of fewer than 3 events (Seckfort et al., 2008). Accordingly, HIV+ and HC participants were grouped as follows: HC Low-ELS ($N = 20$), HC High-ELS ($N = 27$), HIV+ Low-ELS ($N = 24$), and HIV+ High-ELS ($N = 25$). Table 1 details participant group characteristics.

Magnetic Resonance Imaging

Structural images of the brain were obtained using a 3-Tesla scanner (Siemens TIM Trio; Siemens, New York, NY). High-resolution T1-weighted MPRAGE images were acquired in the sagittal plane (resolution = 0.86 mm × 0.86 mm × 0.86 mm; TR = 2250 ms; TE = 3.06 ms; TI = 900 ms; flip angle = 9°; FOV = 220 mm).

Brain volumes were measured using the Individual Brain Atlases using Statistical Parametric Mapping Software (IBASPM) (Alemán-Gómez, Melie-García, & Valdés-Hernández, 2006) toolbox version 1.0 for Statistical Parametric Mapping 5 (SPM5; Wellcome Department of Imaging Science; www.fil.ion.ucl.ac.uk/spm/). Individual brain volumes were segmented into gray matter, white matter, and cerebrospinal fluid and normalized *via* nonlinear registration to the MNI152 template. Volume estimates were calculated for each parcellation as well as for total intracranial volume. Grey matter voxels were then aligned to a map of 116 anatomically labeled structures (Tzourio-Mazoyer et al., 2002), and inverse-transformed into their native spaces, producing volume measurements for individual brain structures in original space based on an MNI anatomical atlas. Brain segmentations were visually inspected for accuracy; none were discarded. Volumetric data were extracted for five regions of interest (ROI) in each hemisphere: ACC, caudate, putamen, hippocampus, and amygdala. We assessed unilateral rather than bilateral ROI volumes given the evidence that ELS may have lateralized effects (Maheu et al., 2010; Stein et al., 1997). All ROI volumes were corrected for total intracranial volume (by dividing each ROI volume by total intracranial volume) before analysis.

Neurocognitive Measures

A brief battery of neuropsychological tests sensitive in detecting HIV-related cognitive impairments (Heaton et al., 1995) was administered to examine abilities in four cognitive domains:

1. *Psychomotor/Processing Speed*: Trail Making Test, Part A (Reitan & Davison, 1974); Wechsler Adult Intelligence Scale III (WAIS-III) Symbol Search and Digit-Symbol Coding (Wechsler, 1997)
2. *Executive Functioning*: Trail Making Test, Part B (Reitan & Davison, 1974); verbal fluency (FAS) (Borkowski, Benton, & Spreen, 1967); WAIS-III Letter-Number Sequencing (Wechsler, 1997)
3. *Fine-motor Dexterity*: Grooved Pegboard Test, dominant and non-dominant hand performance (Klove, 1963)
4. *Verbal Memory*: Hopkins Verbal Learning Test – Revised, total trials 1–3 and delayed recall (Benedict, Schretlen, Groninger, & Brandt, 1998; Brandt & Benedict, 2001).

Raw scores were computed to *Z*-scores based on published normative data (Brandt & Benedict, 2001; Spreen & Strauss, 1998; Tombaugh, 2004; Wechsler, 1997). *Z*-scores for tests in each cognitive domain were averaged to compute a domain-specific composite score for each participant (Castelo, Courtney, Melrose, & Stern, 2007).

Statistical Analyses

One-way analyses of variance (ANOVAs) and χ^2 tests were used to assess differences in demographic variables between the four groups. *Post hoc* comparisons were conducted using a Sidak correction for multiple comparisons. Two-way ANOVAs with factors of HIV-status and ELS-status were

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used to compare the four groups' ROI volumes and cognitive composite scores, and to examine the interaction between HIV-status and ELS-status. Demographic variables that differed significantly between groups were entered as covariates. *Post hoc* comparisons were conducted using independent-samples *t* tests.

Linear regression analyses were conducted to assess the extent to which HIV-disease factors and ELS exposure affected the volumes of those ROIs that differed significantly between groups. Because our aim was to understand the effects of ELS on brain pathology in HIV+ patients, regression analyses were restricted to the HIV+ group. In each model, ROI volumes were entered as the dependent variable, and the independent variables included viral load group (undetectable/detectable), current CD4 count, nadir CD4 count, and ELSQ score. Separate regression analyses were implemented to examine the association between ROI volumes and cognitive functions for those cognitive composites on which significant group differences were observed. We restricted these analyses to the HIV+ group, as our goal was to understand the relation between brain volumes and neurocognitive impairment in HIV+ patients specifically. In these analyses, ROI volumes were entered as independent variables and composite scores were entered as the dependent variable.

RESULTS

Participant Demographics

The four groups were well matched in terms of age ($p = .37$), general cognitive status (MMSE; $p = .60$), estimated premorbid intelligence (WTAR; $p = .16$), proportion of Caucasian to non-Caucasian participants ($\chi^2 = 4.26$; p = .23) and male:female ratio ($\chi^2 = 4.42$; $p = .22$) (Table 1). Groups did not differ significantly on PTSD symptoms (PCLC; $p = .11$). Mean scores on the PTSD scale were below clinically significant levels (<44) for all groups.

Significant group differences were observed on years of education ($F[3,92]=2.87$; $p < .05$), current stress levels ($F[3,91]=4.12$; $p < .01$), current depression symptoms ($F[3,90]=3.93$; $p < .01$), history of cocaine use ($F[3,91]=4.32$; $p < .01$), and proportion of HCV-infected individuals

Table 1. Demographic characteristics of the participant groups

	HC Low-ELS (M/F = 10/10)		HC High-ELS (M/F = 14/13)		HIV+ Low-ELS (M/F = 13/11)		HIV+ High-ELS (M/F = 19/6)	
Variable	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age (years)	45.95	12.78	41.96	10.34	46.92	9.19	44.24	10.34
Education (years)	14.45[a]	3.41	12.59	2.93	12.33[a]	1.69	12.80	2.16
Ethnic composition								
% Caucasian American	80.0		70.4		62.5		52.0	
% African American	10.0		22.2		16.7		32.0	
% Hispanic American	0.0		3.7		8.3		12.0	
% Biracial or "other"	10.0		3.7		12.5		4.0	
% Male	50.0		51.9		54.2		76.0	
MMSE (/30)	28.25	1.07	28.56	1.31	28.46	1.06	28.68	0.80
WTAR (SS)	104.25	16.11	101.81	14.28	95.17	15.40	96.24	16.60
Number of ELS events	1.20[a,b]	0.77	5.30[a,c]	2.23	1.42[c,d]	0.78	4.68[b,d]	1.70
CESD (/60)	10.50[a]	8.17	17.76	15.38	16.42	12.58	24.12[a]	14.19
PSS (/70)	20.75[a]	8.52	22.19	8.86	19.21[b]	7.27	26.83[a,b]	7.59
PCLC (/85)	30.45	14.34	35.04	17.05	35.38	15.00	42.08	17.21
KMSK-Alcohol (/13)	8.00	3.96	10.07	3.54	9.33	4.05	9.17	4.40
KMSK-Cocaine (/16)	3.00[a]	5.11	5.67	6.42	6.88	6.47	9.63[a]	6.54
KMSK-Opiate (/13)	0.15	0.49	1.63	3.35	1.58	3.54	2.96	4.70
HCV-infected (%)	0.0*		14.8		20.8		44.0**	
Length of infection (years)					14.46	6.60	13.04	7.98
Number of patients on cART					21		20	
Nadir CD4 (cells/μl)					167.35	129.59	203.68	191.47
Current CD4 (cells/μl)					560.96	313.51	460.92	257.35
Viral load, Number of patients								
Undetectable (<75 copies/mL)					16		20	
Low (<400 copies/mL)					1		0	
High (>400 copies/mL)					6		4	

Note. HC = Healthy Control; ELS = early life stress; M/F = Male-Female; MMSE = Mini-Mental State Exam; WTAR = Wechsler Test of Adult Reading; SS = Standard Score; CESD = Center for Epidemiologic Studies Depression Scale; PSS = The Perceived Stress Scale; PCLC = PTSD Checklist—Civilian; KMSK = Kreek-McHugh-Schluger-Kellogg scale; HCV = hepatitis C virus; cART = combination antiretroviral therapy. Across rows, means with the same superscript are significantly different at the $p < .05$ level. Asterisks indicate that the reported value significantly deviates from expected values as determined by the chi-square test, *$p \leq .05$, **$p \leq .01$.

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Table 2. Mean ROI volumes (cm^3) for each group

	HC Low-ELS		HC High-ELS		HIV+ Low-ELS		HIV+ High-ELS	
Brain region	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Right amygdala	1.65	0.17	1.62[a]	0.22	1.67[b]	0.26	1.70[a,b]	0.17
Left amygdala	1.38[a]	0.13	1.43[b]	0.19	1.44[c]	0.20	1.47[a,b,c]	0.15
Right ACC	3.91	0.62	4.10	0.98	3.66	0.69	3.68	0.67
Left ACC	4.30	0.80	4.68	1.18	4.35	0.97	4.24	0.73
Right hippocampus	4.17	0.50	4.21	0.80	4.34	0.75	4.36	0.56
Left hippocampus	4.39	0.59	4.43	0.83	4.60	0.88	4.50	0.62
Right caudate	4.16	0.70	4.13	0.67	4.36	0.86	4.27	0.70
Left caudate	4.03	0.65	3.91	0.58	4.03	0.76	4.06	0.85
Right putamen	3.73	0.58	3.82	0.74	3.95	0.66	3.96	0.54
Left putamen	3.94	0.60	4.05	0.78	4.15	0.75	4.17	0.66

Note. ROI = region of interest; HC = healthy control; ELS = early life stress; ACC = anterior cingulate cortex. Across rows, means with the same superscript differ significantly ($p < .05$) after correcting for total intracranial volume.

($\chi^2 = 13.99$; $p < .01$). *Post hoc* analyses indicated that HC Low-ELS reported higher education levels compared with HIV+ Low-ELS ($p = .05$). HIV+ High-ELS reported greater current stress levels than HIV+ Low-ELS ($p < .01$). Depression levels were higher in HIV+ High-ELS compared with HC Low-ELS ($p < .01$); mean CESD scores were above the cut-off score (>15), indicating significant depression levels, in all groups except HC Low-ELS. Lifetime history of cocaine use was higher in HIV+ High-ELS compared with HC Low-ELS ($p < .01$); however, mean KMSK-C scores were below clinical dependence levels (KMSK-C > 10) for all four groups, as were mean scores for alcohol and opiate use (KMSK-A > 10; KMSK-O > 8). HC Low-ELS contained a significantly low number of HCV-infected individuals ($Z = -2.0$, $p = .05$), and HIV+ High-ELS contained a significantly high number of HCV-infected individuals ($Z = 2.5$; $p = .01$).

HIV+ High-ELS and HIV+ Low-ELS were not significantly different with respect to years diagnosed, current CD4 counts, nadir CD4 levels (all t's < 1.22, p's > .23), proportion of individuals with detectable viral loads ($\chi^2 = .59$; $p = .44$), or percent of participants on cART (Fisher's exact test; $p = .70$).

MRI Volumetrics

Mean ROI volumes for each group are shown in Table 2. Intracranial volumes did not differ significantly between groups ($F[3,92] = .13$; $p = .94$), permitting valid group comparisons using intracranial-corrected ROI volumes. Significant group differences were observed in the right and left amygdala (described below). Analyses in all additional ROIs were non-significant ($p > .05$).

In the right amygdala ($F[3,92] = 2.94$; $p = .04$), we observed a significant interaction between HIV and ELS ($F[1,92] = 4.53$; $p = .04$), and a marginally significant main effect of HIV ($F[1,93] = 3.92$; $p = .07$), indicating that right amygdala volumes in HIV+ were significantly larger than those in HC ($t[83.9] = 2.00$; $p = .05$). These effects were significant (HIV: $F[1,83] = 7.42$; $p < .01$; HIV-ELS interaction: $F[1,83] = 5.04$; $p = .03$) even after controlling for group differences in education, current stress, depression, cocaine use history, and HCV status. To investigate the source of the HIV-ELS interaction, we conducted follow-up analyses, which revealed that the interaction was driven by higher volumes in HIV+ High-ELS compared with HIV+ Low-ELS ($t[47] = 2.13$; $p = .04$; $r = .30$) and HC High-ELS ($t[50] = 2.84$; $p < .01$, $r = .37$) (Figure 1).

In the left amygdala ($F[3,92] = 3.27$; $p = .02$), we observed significant main effects of HIV ($F[1,92] = 5.88$; $p = .02$) and ELS ($F[1,92] = 3.90$; $p = .05$), indicating that left amygdala volumes for HIV+ were significantly larger than those of HC, and that left amygdala volumes in the High-ELS group were larger than those in the Low-ELS group. These effects were maintained (HIV: $F[1,83] = 8.42$; $p < .01$; ELS: $F[1,83] = 5.56$; $p = .02$) even after controlling for group differences in education, current stress, depression, cocaine use history, and HCV status. To further clarify the main effects, independent-samples t tests were conducted, which indicated that the group effects were driven by significant left amygdala enlargement in HIV+ High-ELS compared with HIV+ Low-ELS ($t[47] = 2.00$; $p = .05$; $r = .28$), HC High-ELS

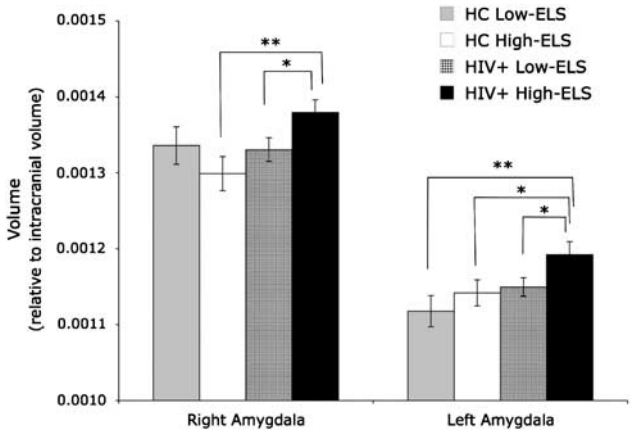

Fig. 1. Mean (+SEM) amygdala volume measures (corrected for intracranial volume) for each group. *Note:* *$p \leq .05$, **$p < .01$.

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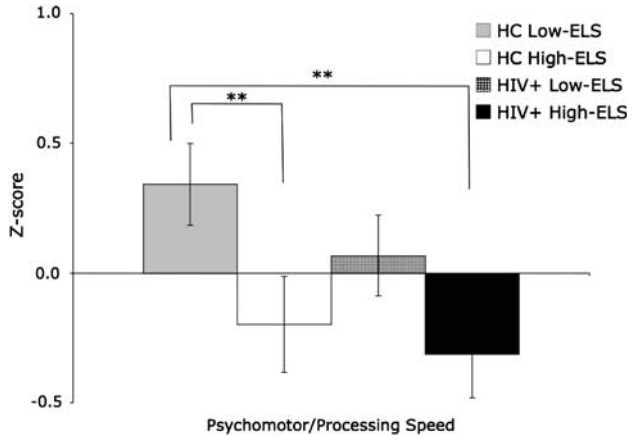

Fig. 2. Mean (+SEM) group scores on the psychomotor/processing speed composite index. *Note:* $^{**}p \leq .01$.

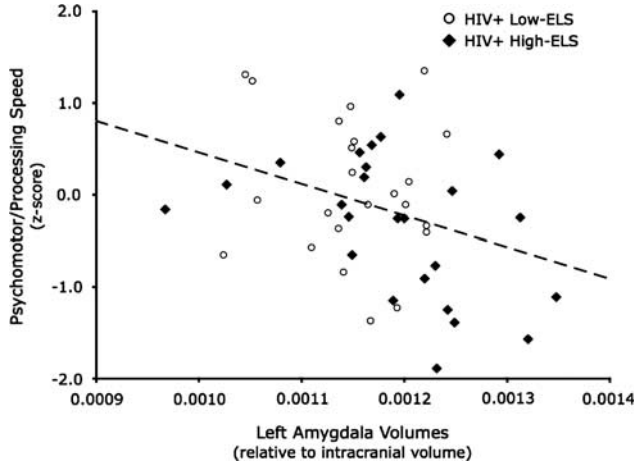

Fig. 3. Correlations between left amygdala volumes (corrected for intracranial volume) and psychomotor/processing speed composite scores in the HIV+ group.

($t[50]=2.05$; $p = .04$; $r = .28$), and HC Low-ELS ($t[43] = 2.81$; $p < .01$; $r = .39$) (Figure 1).

Neurocognitive Measures

Analyses of the groups' performances on the psychomotor/processing speed composite measure ($F[3,91]=3.47$; $p = .02$) revealed a significant main effect of ELS ($F[1,91]=9.06$; $p < .01$). This effect was maintained ($F[1,82]=3.36$; $p = .07$) even after controlling for group differences in education, current stress, depression, cocaine use history, and HCV status. To further delineate the effect of ELS we conducted *post hoc* analyses, which revealed that participants in the HIV+ High-ELS and HC High-ELS groups were significantly slower on these measures compared with HC Low-ELS ($t[43]=2.89$; $p < .01$; $r = .40$; $t[45]=2.58$; $p = .01$; $r = .36$, respectively) (Figure 2). No additional significant group differences in composite scores were observed.

Relation of HIV-Disease Factors and ELS Exposure to ROI Volumes

The relation of amygdala volumes to HIV-disease factors (i.e., viral load, current CD4, nadir CD4) and ELS exposure (ELSQ score) in HIV+ was examined using linear regression. In the right amygdala we observed a trend level effect for ELS scores [$\beta = .28$ ($t = 1.85$; $p = .07$)], indicating that greater ELS exposure was associated with larger right amygdala volumes. In the left amygdala, enlargement was significantly associated with higher ELS scores [$\beta = .39$ ($t = 2.59$; $p = .01$)] and lower nadir CD4 counts (i.e., poorer historical immunological health) [$\beta = -.40$ ($t = -2.24$; $p = .03$)]. No additional variables were significant.

Relation of ROI Volumes to Neurocognitive Functions

A linear regression analysis was conducted to examine the relation between amygdala volumes and psychomotor/processing speed in HIV+ participants. Left amygdala volumes were significant [$\beta = -.34$ ($t = -2.24$; $p = .03$)] in the resulting model, revealing that greater left amygdala volumes were associated with reduced psychomotor/processing speed (Figure 3), whereas right amygdala volumes were non-significant [$\beta = .01$ ($t = .08$; $p = .94$)]. Left amygdala volumes accounted for 10% of the variance in psychomotor/processing speed performance. This finding was maintained even after controlling for education, current stress, depression, cocaine use history, and HCV status [left amygdala: $\beta = -.34$ ($t = -2.25$; $p = .03$)]. Pearson correlations revealed that this relation was significant in HIV+ High-ELS ($r = -.41$; $p = .04$), but not in HIV+ Low-ELS ($r = -.12$; $p = .60$), HC High-ELS ($r = .25$; $p = .21$), or HC Low-ELS ($r = .29$; $p = .22$). However, Fisher's r-to-z transformation showed that the correlation in HIV+ High-ELS was significantly different from HC Low-ELS ($Z = -2.26$; $p = .01$) and HC High-ELS ($Z = -2.33$; $p < .01$), but not HIV+ Low-ELS ($Z = -1.03$; $p = .15$).

Lastly, to exclude the possibility that the observed relation between left amygdala volumes and psychomotor/processing speed could result from shared variance between left amygdala and caudate or putamen volumes, which have been shown to be related to psychomotor/processing speed impairments in HIV+ patients (Castelo et al., 2007; Paul et al., 2002), a regression analysis controlling for volumes of these structures was conducted. The results revealed a significant association between left amygdala volumes and psychomotor/processing speed performance [$\beta = -.41$ ($t = -2.37$; $p = .02$)] even after controlling for caudate and putamen volumes.

DISCUSSION

To our knowledge, this is the first study conducted to examine whether high ELS is associated with increased HIV-related brain abnormalities in HIV+ adults. We report that HIV infection and high ELS exposure have combined effects

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on amygdala volumes and cognitive function, as HIV+ High-ELS individuals demonstrated larger amygdala volumes and greater impairment on tests of psychomotor/processing speed. Collectively, our results provide strong evidence that high ELS contributes significantly to structural brain and neurocognitive abnormalities in HIV+ patients.

More specifically, we found that HIV+ participants demonstrated greater amygdala volumes compared with HIV-seronegative participants – an effect that was strongly driven by the HIV+ HIGH-ELS group. Our observation of amygdala enlargement in HIV+ patients is novel and parallels prior results indicating HIV-related volumetric increases in other subcortical regions (Castelo et al., 2007). While there is prior evidence of HIV-related abnormalities in temporal limbic regions (Jernigan et al., 1993), there is little to no data regarding HIV-related structural changes in the amygdala specifically. Thus, the results of this study enhance our understating of the effects of HIV on the amygdala. Furthermore, our finding of an ELS effect on the amygdala is in direct agreement with recent findings indicating a positive correlation between ELS exposure and amygdala volumes in children whose HIV status was not examined (Tottenham et al., 2009). Our study extends this literature, as it provides evidence that ELS-related abnormalities in the amygdala remain years after the stressors have been experienced, consistent with results from animal studies revealing enduring stress-related structural changes in the amygdala (Vyas, Pillai, & Chattarji, 2004).

We found that both lower nadir CD4 levels and higher ELS exposure significantly predicted amygdala enlargement in HIV+ participants. These results provide strong evidence that both HIV infection and ELS history influence amygdala morphometry in HIV+ patients. The broader implication of these findings is that high ELS may produce changes in the amygdala that predispose individuals to experiencing greater HIV-related neuropathological effects in this region. Several converging lines of evidence indicate that the amygdala is sensitive to the long-term effects of stress (Baram & Hatalski, 1998; Kikusui & Mori, 2009; Mehta et al., 2009; Ono et al., 2008; Payne, Machado, Bliwise, & Bachevalier, 2010; Salzberg et al., 2007; Tottenham et al., 2009; Tottenham & Sheridan, 2010; Vyas et al., 2004). In addition, the amygdala undergoes rapid changes in early life (Baram & Hatalski, 1998; Payne et al., 2010), which may increase its susceptibility to adverse conditions during this period (Tottenham & Sheridan, 2010). Animal studies have demonstrated that the amygdala can sustain both structural (e.g., accelerated amygdala myelination, increased dendritic arborization) and functional (e.g., hyper-sensitization) changes in response to ELS (Baram & Hatalski, 1998; Brown, 2000; Kikusui & Mori, 2009; Ono et al., 2008; Payne et al., 2010; Salzberg et al., 2007; Tottenham & Sheridan, 2010), which persist even under improved environmental conditions (Vyas et al., 2004). Hence, it is possible that such changes may increase vulnerability to HIV-related neuropathology occurring in temporal limbic regions (Jernigan et al., 1993), leading to the observed amygdala enlargements in HIV+ High-ELS individuals. Our findings, taken together with those of previous studies indicating the susceptibility of the amygdala to ELS, strengthen the suggestion that the amygdala can undergo significant morphologic changes secondary to "legacy" events, such as those associated with HIV infection (i.e., reductions in nadir CD4) or high ELS exposure, which are resistant to recovery even after the causative agent has resolved.

Our study revealed that greater left amygdala enlargement in HIV+ participants was associated with greater impairment on tests of psychomotor and processing speed, illustrating the clinical significance of amygdala enlargements in HIV+ patients, especially those with high ELS. The observation that amygdala volumes may affect cognitive processing speed in HIV+ patients is compelling. While the amygdala is typically considered an affective brain region (Dolan & Vuilleumier, 2003; Liberzon, Phan, Decker, & Taylor, 2003), its activity can also impact cognitive functions (Drevets & Raichle, 1998; Ledoux, Lane, & Nadel, 2000; Yamasaki, LaBar, & McCarthy, 2002; Yun, Krystal, & Mathalon, 2010). These effects are believed to occur through rich connections between the amygdala and frontal-lobe regions responsible for higher-order cognitive functions (Amaral & Price, 1984; Barbas & De Olmos, 1990; Blair et al., 2007; Drevets & Raichle, 1998; Ghashghaei & Barbas, 2002; Hariri, Bookheimer, & Mazziotta, 2000; Pessoa, 2008, 2010; Price, 2003; Quirk, Likhtik, Pelletier, & Pare, 2003; Stefanacci, Suzuki, & Amaral, 1996; Stein et al., 2007; Yamasaki et al., 2002; Yun et al., 2010). Accordingly, our observed relation between left amygdala hypertrophy and reduced processing speed in HIV+ participants could result from abnormalities within amygdala-frontal lobe networks (Drevets & Raichle, 1998; Ledoux et al., 2000; Yamasaki et al., 2002; Yun et al., 2010)—a notion that is supported by evidence indicating a relation between left (but not right) amygdala-frontal lobe connectivity and cognitive performance (Yun et al., 2010). Future studies using functional MRI methods will be best to address this hypothesis.

As a whole, our HIV+ cohort did not display significant cognitive abnormalities compared to the HC group. However, we did observe marked differences in processing speed between the HIV+ High-ELS and HC Low-ELS groups, as HIV+ High ELS participants demonstrated mild impairment in this domain. The lack of an overall HIV effect is not surprising given recent findings in other samples of relatively healthy HIV+ patients on stable cART, indicating that cognitive impairments are commonly mild or even absent in such cohorts (Heaton et al., 2010, 2011; Melrose et al., 2008; Towgood et al., 2012). The fact that cognitive abnormalities were not detected in the HIV+ Low-ELS group underscores the potential importance of high ELS as a contributory factor in the emergence of cognitive decline in HIV+ patients. Notably, stress has been identified as an important precipitating agent in other neurodegenerative disorders (e.g., Alzheimer's disease) (Tran, Srivareerat, & Alkadhi, 2010; Wilson et al., 2006). Such findings implicate high ELS as a risk factor for developing more rapid decline over time in HIV-infected individuals. While the current study cannot

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address this question, future longitudinal studies may provide more clarity on this possibility.

Several issues warrant further consideration. First, as with most research relying on retrospective reports, accurate quantification of ELS in the current study may be complicated by participant bias, revisionist recall error, and normal forgetting (Hardt & Rutter, 2004; Maughan & Rutter, 1997). Prospective studies of the effects of ELS on the brain are preferable, but this is less feasible in adult cohorts. That our ELS-related findings in the amygdala are in line with those observed in studies involving children, in which ELS was more discretely quantified (Mehta et al., 2009; Tottenham et al., 2009), provides some assurance against the possibility that our results may be driven by retrospective bias (e.g., that participants with larger amygdalae would have a greater tendency to endorse ELS-related events retrospectively).

Second, our observation of ELS-related effects in the amygdala differs from a previous study, conducted in an adult population, that reported non-significant differences in amygdala volumes between "no-ELS" and "high-ELS" groups (Cohen, Grieve, et al., 2006). The divergent findings are likely attributable to our inclusion of HIV+ patients, given that our ELS effect was driven by the HIV+ High-ELS group and that amygdala volumes in HC High-ELS and HC Low-ELS did not differ. This suggests that in adults [as opposed to children in whom acute effects of high ELS can be observed volumetrically (Mehta et al., 2009; Tottenham et al., 2009)] the effect of high ELS may be expressed as an increase in the susceptibility of the amygdala to later insults (e.g., HIV), while high ELS exposure *alone* may not be sufficient enough to result in significant amygdala enlargement. This is consistent with the results of Cohen, Grieve, et al. (2006), and in line with studies indicating that high ELS can confer a latent risk for negative health outcomes in later adulthood (Taylor, 2010).

Third, high ELS in the current study was defined as exposure to several different adverse events that may not be easily equated across individuals, and therefore, a simple summation of their effects is admittedly complex. Future studies should examine whether specific types of events [e.g., abuse (Andersen et al., 2008)], experienced within specific developmental periods, may have stronger neurological influences than others. Yet, there is evidence that adverse childhood events commonly co-occur (Dong et al., 2004). Accordingly, an assessment of a wide diversity of adverse events is likely beneficial, as this permits 1) a more comprehensive examination of early-life environmental conditions that have potential to impact the brain and 2) an examination of the possible additive effects of such events. Our results, in combination with prior findings (Cohen, Grieve, et al., 2006; Hedges & Woon, 2011; Paul, Henry, et al., 2008; Seckfort et al., 2008; Tomalski & Johnson, 2010), indicate that ELS history, as a broadly encompassing construct, deserves serious consideration as an important etiological factor with the potential to influence neural development and function over a lifetime. Such findings align well with a rapidly expanding literature documenting the negative effects of high ELS on a variety of health outcomes in adults (e.g., cancer, stroke, heart disease) (Chen, Matthews, & Boyce, 2002; Dube, Felitti, Dong, Giles, & Anda, 2003; Felitti et al., 1998; Gilbert et al., 2009; Repetti, Taylor, & Seeman, 2002; Smith, Hart, Blane, & Hole, 1998; Taylor, 2010).

Lastly, our groups differed with respect to education, current stress, depression, lifetime cocaine use, and HCV status. Although our analyses indicated that group differences in these variables did not account for amygdala volume abnormalities or reduced psychomotor/processing speeds observed in the HIV+ High-ELS group, it remains possible that these demographic differences may have an indirect influence on our findings. Future studies should investigate the brain effects of HIV and ELS in samples in which these demographic variables are more systematically controlled. Similarly, while our sample size is comparable to neuroimaging studies of this type (e.g., Castelo et al., 2007; Towgood et al., 2012), it would be useful to replicate our findings in a larger sample.

In conclusion, our data suggest that high levels of ELS exposure may be a significant risk factor for HAND, as we observed that high ELS is associated with increased neurological (i.e., amygdala) and neurocognitive abnormalities in HIV+ patients. This is the first evidence suggesting that significant exposure to ELS may contribute to cognitive impairment in adults presenting with an underlying neurological vulnerability (i.e., HIV). Notably, these findings suggest that high ELS deserves careful consideration as an important etiological factor in the development of neurodegenerative disease processes observed in adulthood (e.g., HAND, Alzheimer's disease, etc.). In the case of HIV, additional studies are needed to determine whether high ELS and HIV contribute to increased neuropathology through additive, independent effects on the amygdala, or if high ELS and HIV interact synergistically at a more biological level [e.g., both acting to decrease immune system health and/or increase proinflammatory cytokine activity (Boyce et al., 1995; Glaser, Rice, Speicher, Stout, & Kiecolt-Glaser, 1986; Leserman, 2003, 2008; Miller, Cohen, & Ritchey, 2002; Zachariae, 2009)] to result in increased brain pathology. Such studies will likely lead to improvements in the detection and treatment of patients at risk for developing HAND by identifying possible biomarkers (e.g., cytokines) that may help to better classify patients at risk for developing HAND, as well as identifying those biomarkers that may be targeted pharmacologically in an effort to reduce HAND.

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