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High Early Life Stress and Aberrant Amygdala Activity: Risk Factors for Elevated Neuropsychiatric Symptoms in HIV+ Adults

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Abstract

Relative to HIV-negative adults, HIV+ adults report elevated levels of early life stress (ELS). In non-HIV samples, high ELS has been linked to abnormalities in brain structure and function, as well as increased risk of neuropsychiatric symptoms. Yet, little is known about the neural effects of high ELS, and their relation to elevated neuropsychiatric symptoms, in HIV+ adults. Recent studies have revealed combined effects of HIV and high ELS on amygdala morphometry. Aberrant amygdala activity is prominently implicated in studies of neuropsychiatric symptomology in non-HIV samples. Hence, this preliminary study examined: 1) the combined effects of HIV and high ELS on amygdala activity, and 2) the relation between amygdala activity and neuropsychiatric symptoms in HIV+ adults. We included 28 HIV+ adults and 25 demographically-matched HIV-negative control (HC) adults. ELS exposure was quantified using a retrospective ELS questionnaire, which defined four groups: HIV+ Low-ELS (N=15); HIV+ High-ELS (N=13); HC Low-ELS (N=16); and HC High-ELS (N=9). Participants completed a battery of neuropsychiatric measures. BOLD fMRI assessed amygdala reactivity during explicit observation of fearful/angry faces. High-ELS participants demonstrated reduced levels of amygdala reactivity relative to Low-ELS participants. HIV+ High-ELS participants reported higher levels of neuropsychiatric symptoms than all other groups. In the HIV+ group, lower amygdala responses were associated with higher neuropsychiatric symptoms, particularly depression, anxiety, and alexithymia. Collectively, these results suggest that high ELS exposure is a significant risk factor for

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Compliance with Ethical Standards

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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neuropsychiatric symptoms in HIV+ adults. Furthermore, our results implicate ELS-related abnormalities in amygdala activity in the etiology of neuropsychiatric symptoms in HIV+ adults.

Keywords

Amygdala; Adverse Childhood Experiences; Childhood Abuse; Childhood Trauma; Depression; Anxiety; Alexithymia

Introduction

Compared to HIV-negative adults, HIV-positive (HIV+) adults report higher rates of neuropsychiatric symptoms across a broad range of domains, with significant increases in depression, anxiety, apathy, alexithymia, and interpersonal problems (Benton 2008; Bing et al. 2001; Bogdanova et al. 2010; Ciesla and Roberts 2001; Clark et al. 2010a; Do et al. 2014; Morrison et al. 2002). There is growing evidence that levels of early life stress (ELS) exposure are also elevated in HIV+ cohorts relative to non-HIV samples (Machtinger et al. 2012; Paxton et al. 2004; Spies et al. 2012). Estimated rates of ELS exposure in HIV+ cohorts range from 32% to 76% (Simoni and Ng 2000; Spies et al. 2012; Villar-Loubet et al. 2014; Walton et al. 2011; Whetten et al. 2006), compared to 14% to 32% reported in non-HIV samples (Spies et al. 2012). The high prevalence of ELS events among HIV+ adults necessitates a greater understanding of the independent and combined effects of HIV infection and high ELS on mental health outcomes. High ELS exposure is associated with an increased risk of neuropsychiatric symptoms in non-HIV adult samples (Dube et al. 2003; Felitti et al. 1998; Kaufman and Charney 2001; McFarlane et al. 2005; Pechtel and Pizzagalli 2011; Pesonen and Raikkonen 2012; Repetti et al. 2002; Taylor 2010). In addition, neuroimaging studies indicate that high ELS exposure has lasting effects on brain regions implicated in affect regulation in non-HIV samples (Andersen et al. 2008; Baker et al. 2013; R. A. Cohen et al. 2006a; Dannlowski et al. 2012; Evans et al. 2015; Grant et al. 2011; Mehta et al. 2009; Taylor et al. 2006; Teicher et al. 2002; Tottenham et al. 2009a). Despite this evidence, research examining the neuropsychiatric sequelae of high ELS in the context of HIV infection is sparse. Moreover, we do not yet have a full appreciation of the degree to which neuropsychiatric symptoms in HIV+ cohorts stem from ELS-related or HIV-related factors.

Although the etiology of neuropsychiatric difficulties in HIV+ adults is still poorly understood, there is evidence that HIV-related neural abnormalities may play a contributory role. Results from neuroimaging studies point to both functional and structural abnormalities, such as abnormalities in serotonergic transmission (Hammoud et al. 2010), cortical and subcortical white matter (Smith et al. 2008; Stubbe-Drager et al. 2012), and grey matter volumes (Clark et al. 2015; Paul et al. 2005). In addition, some studies have observed significant associations between volumetric abnormalities in affective brain regions and markers of historical HIV-disease severity (e.g., nadir CD4 levels, the lowest ever T-cell count on record) (Clark et al. 2012; Clark et al. 2015). Taken together, these studies suggest that neuropsychiatric disorders in HIV+ adults may reflect a direct manifestation of the disease and its impact on neural systems involved in affect regulation.

Further elucidating the neural substrates of neuropsychiatric symptoms in HIV+ adults is of great importance, as the burden of neuropsychiatric disorders in this population is high. Moreover, neuropsychiatric disorders have a negative effect on critical HIV-disease outcomes (e.g., medication adherence) and have been linked to increased HIV-related mortality rates (Antelman et al. 2007; Catz et al. 2000; Cook et al. 2002; Horberg et al. 2008; Ickovics et al. 2001; Leserman 2008; Marshall et al. 2013; Mayne et al. 1996; Panos et al. 2014; Safren et al. 2001). Gaining a better understanding of the neural substrates of these highly prevalent disorders could stimulate improvements in diagnostic, preventative, and treatment strategies available to HIV+ adults, which in turn would improve both quality of life and health outcomes in this population. Furthermore, studies that begin to tease apart the effects of HIV and high ELS exposure on brain function and mental health outcomes could potentially enhance these pursuits by providing greater specificity regarding the demographic and neurobiological factors associated with elevated neuropsychiatric symptoms in HIV+ adults.

To our knowledge, only two studies have explored the combined effects of HIV infection and high ELS exposure on the brain (Clark et al. 2012; Spies et al. 2015). Findings from each of these studies suggest synergistic effects of HIV and high ELS on amygdala morphometry. The amygdala is important to a variety of neuropsychiatric and psychosocial functions (Bickart et al. 2014; Hilbert et al. 2014; Murray et al. 2011; Whalen and Phelps 2009). Moreover, converging data implicate amygdala abnormalities in the development and course of neuropsychiatric disorders in non-HIV samples (Blair et al. 2008; Etkin and Wager 2007; Groenewold et al. 2013; Li et al. 2014; Schienle et al. 2011). For example, abnormal levels of amygdala activation are commonly observed in adults with depression or anxiety (Damsa et al. 2009; Groenewold et al. 2013; Holzschneider and Mulert 2011), and there is evidence that amygdala responses normalize to some degree upon remission of these conditions (Arnone et al. 2012; Sheline et al. 2001). Overall, there has been minimal investigation of the amygdala in HIV+ cohorts, with most studies focusing on morphologic abnormalities (Ances et al. 2012; Behrman-Lay et al. 2015; Clark et al. 2012; Clark et al. 2015; Ortega et al. 2013; Spies et al. 2015). Hence, it remains unclear whether abnormalities in amygdala activation occur in HIV+ samples, and whether these abnormalities contribute to greater levels of neuropsychiatric symptoms in this patient population. Given prior observations of abnormal amygdala activity in non-HIV adult samples with high ELS (Dannlowski et al. 2012; Evans et al. 2015; Grant et al. 2011; Taylor et al. 2006), coupled with the high burden of ELS exposure in HIV+ cohorts, understanding the potential contribution of amygdala activity to neuropsychiatric symptoms in HIV+ adults appears particularly relevant. Yet, the combined effects of HIV and high ELS on amygdala activity, and the relation between amygdala activity and neuropsychiatric symptoms in HIV+ cohorts have not been investigated previously.

The current study was conducted to further elucidate the neural substrates of neuropsychiatric symptoms in HIV+ adults. We had two goals in conducting this preliminary study. Our first goal was to use functional magnetic resonance imaging (fMRI) to examine the independent and combined effects of HIV status and high ELS exposure on amygdala activity. Based on prior findings (Clark et al. 2012), we were particularly interested in assessing the effect of high ELS on amygdala activity in HIV+ adults. We

hypothesized that HIV+ adults would exhibit abnormalities in amygdala reactivity relative to HIV-negative adults, and that HIV+ adults with high ELS would exhibit greater abnormalities than HIV+ adults with low ELS. The second goal was to examine whether abnormalities in amygdala reactivity, if present in HIV+ adults, were associated with elevated neuropsychiatric symptoms in our HIV+ sample. We assessed a number of symptoms commonly endorsed by HIV+ adults, including levels of depression, anxiety, apathy, alexithymia, and interpersonal problems (Benton 2008; Bing et al. 2001; Bogdanova et al. 2010; Ciesla and Roberts 2001; Clark et al. 2010a; Do et al. 2014; Fleishman et al. 2000; Hudson et al. 2001; Kamat et al. 2012; Morrison et al. 2002). Before assessing whether amygdala reactivity levels were associated with neuropsychiatric symptoms in HIV + adults, we first determined whether HIV+ adults in our sample did indeed report experiencing greater neuropsychiatric symptoms. Here too, we sought to examine the effects of high ELS status on symptom levels in our HIV+ group. We hypothesized that HIV+ adults would report higher levels of neuropsychiatric symptoms relative to HIV-negative adults, and that this effect would be greatest in HIV+ adults with high ELS. We further hypothesized that degree of amygdala reactivity would covary with levels of neuropsychiatric symptoms in HIV+ adults, where greater abnormalities in amygdala reactivity would correlate with higher neuropsychiatric symptom levels.

Methods

Participants

This fMRI study included 28 HIV+ and 25 age-matched HIV-negative control (HC) adults. HIV+ participants were recruited from The Miriam Hospital in Providence, RI and from the Icahn School of Medicine at Mount Sinai in New York, NY. HC participants were recruited from the community at both sites (Table 1). One investigator (USC) oversaw all recruitment and testing procedures. Inclusion criteria were right-handedness, completion of 8 or more years of education, and being a native English speaker. All participants achieved a score of ≥ 25 points on the Mini-Mental Status Exam (MMSE) (Folstein et al. 1975). Exclusion criteria included reported history of uncorrected abnormal vision; developmental disability; learning disability; major psychiatric illness (e.g., schizophrenia, bipolar disorder, posttraumatic stress disorder); neurological illness affecting the central nervous system (e.g., stroke, progressive multifocal leukoencephalopathy, Parkinson's disease); and traumatic head injury with loss of consciousness >10 minutes. Substance use exclusion criteria were reported current alcohol dependence; use of heroin/opiates or any intravenous drug within the past 6 months; use of cocaine within the past 3 months; and positive urine toxicology prior to MRI assessment (cocaine, opiates, methamphetamine, amphetamine, benzodiazepine, barbiturates, methadone, oxycodone). Individuals who tested positive for marijuana use (N=6) were not excluded. The Miriam Hospital's Institutional Review Board and the Icahn School of Medicine at Mount Sinai's Institutional Review Board approved this research. All participants gave their informed consent and were financially compensated for their time.

Demographic Measures

Disease duration in the HIV+ group was estimated using self-report and verified against the medical record. History of antiretroviral (ARV) use, current CD4 levels, nadir CD4 levels

(i.e., the lowest ever T-cell count on record), and viral loads were obtained from medical records. All but one HIV+ participant was prescribed ARV medications. Current CD4 levels ranged from 84 to 1509 cells/μl. Nadir CD4 levels ranged from 2 to 834 cells/μl. HIV viral load was log 10 transformed to normalize the distribution. Alcohol and drug use histories for all participants were quantified using the Kreek-McHugh-Schluger-Kellogg scale (KMSK) (Kellogg et al. 2003), which provided 3 subscales characterizing lifetime consumption of alcohol (KMSK-A), cocaine (KMSK-C), and opiates (KMSK-O). See Table 1 for group characteristics.

Early Life Stress Quantification

ELS exposure was quantified using the Early Life Stress Questionnaire (ELSQ) (R. A. Cohen et al. 2006b), which assessed the occurrence of 17 adverse childhood experiences (ACEs) (e.g., physical abuse, sexual abuse, neglect, family conflict, bullying) prior to age 18 years. HIV+ and HC participants were identified as having either high ELS or low ELS exposure based on their ELSQ responses. Although some studies examining ELS-related neural effects have compared individuals with no ELS exposure (i.e., zero ACEs) to individuals with high ELS (e.g., 3 or more ACEs) (R. A. Cohen et al. 2006a; Paul et al. 2008), this method has not been well suited to our HIV+ samples. We have found that less than 10% of our HIV+ participants report zero ACEs (Clark et al. 2012), consistent with rates observed in prior US studies (Mugavero et al. 2006). In the current sample only 2 HIV + adults (7%) reported zero ACEs. Accordingly, low ELS was classified by endorsement of fewer than 3 ACEs, and high ELS was defined as an endorsement of 3 or more ACEs. Our use of this cutoff score is in line with prior studies examining ELS-related neural abnormalities in HIV+ cohorts and non-HIV samples (Clark et al. 2012; R. A. Cohen et al. 2006a; Paul et al. 2008; Seckfort et al. 2008). Using these criteria, four HIV-ELS groups were classified as follows: HIV+ Low-ELS (N=15); HIV+ High-ELS (N=13); HC Low-ELS (N=16); and HC High-ELS (N=9). Importantly, participants from all four groups were well represented at both testing sites (Table 1).

fMRI Task of Amygdala Reactivity

A block design paradigm known to elicit robust blood oxygen level dependent (BOLD) response in bilateral amygdala was employed during fMRI (Lieberman et al. 2007). This paradigm consisted of five discrete tasks during which participants viewed images of faces expressing negative emotion (anger or fear) (Tottenham et al. 2009b) or shapes. For the purposes of this study, we examined amygdala responses during one of the tasks, the Observe task, because it elicits the strongest degree of amygdala activation relative to the other four tasks in the paradigm (emotion-labeling, gender-labeling, emotion-matching, shapes-matching) (Lieberman et al. 2007). During the Observe task participants viewed a series of single emotional faces, which expressed anger or fear. Each task block began with a 3-second instruction screen (indicating the task type), followed by ten 5-second trials of that task (e.g., presentation of a single face). Trials within each block (5 fearful; 5 angry) were presented in random order using E-Prime software (http://www.pstnet.com). Each 50-second task block was followed by a 10-second fixation crosshair (rest). Participants completed two fMRI image acquisition runs of this paradigm, with one block of each of the five tasks occurring once per run in a counterbalanced order. Each run lasted 5′15″.

MRI Image Acquisition

Whole-brain echoplanar BOLD fMRI was conducted in Providence, RI and New York, NY using the same affective paradigm (described above). At both sites, whole-brain echoplanar BOLD images were acquired in the axial plane with AP phase encoding using a Siemens (Erlangen, Germany) 3 Tesla scanner and a 32-channel head coil. In Providence, RI images were acquired on a Siemens TIM TRIO 3T scanner (TE/TR=28/2500 ms, matrix=64×64 in 3 mm slices, FOV=192×192 mm). This procedure yielded 129 whole-brain volumes for each imaging run with a spatial resolution of 3 mm^3 per voxel. In New York, NY images were acquired on a Siemens MAGNETOM Skyra 3T scanner (TE/TR=35/1000 ms, matrix=108×108 in 2.1 mm slices, FOV=228×228 mm). This procedure yielded 320 whole-brain volumes for each imaging run with a spatial resolution of 2.1 mm^3 per voxel. At both sites, whole-brain high-resolution T1 images were acquired in the sagittal plane prior to the BOLD fMRI scans for anatomical reference (Providence, RI: TE/TR=2.98/1900 ms, 1 mm^3, FOV=256×256 mm; New York, NY: TE/TR=2.07/2400 ms, 0.8 mm^3, FOV=256×256 mm).

fMRI Data Analyses

All fMRI dataset processing and statistical analyses were performed with Analysis of Functional NeuroImages (AFNI) software (Cox 1996). For each run, the 3D+time datasets were slice-timing corrected, spatially aligned to the seventh volume (to minimize movement artifact), coregistered to high-resolution anatomical volumes, and transformed into standard stereotaxic space (Talairach and Tournoux 1988) before a three-dimensional 6-mm Gaussian kernel was applied. Data regarding participant movement were examined; none exhibited excess movement (i.e., movement greater than the spatial resolution of one voxel) during either run. General linear modeling (GLM) was utilized to quantify task specific activity for each brain voxel of individual datasets. The dependent variable in these single-subject analyses was BOLD signal over time; each of the five paradigm tasks (i.e., observe, emotion-labeling, etc.) was modeled as a fixed-response waveform convolved with the hemodynamic response (modeled as a gamma function); additional regressors included instruction screens, covariates (observed movement, linear drift), and resting baseline. For each participant, a general linear test (GLT) was used to compare brain responses during the Observe task to brain responses during rest. Brain regions demonstrating significant task-related effects during the Observe task (relative to rest) were identified using a whole-brain voxelwise one-sample t-test against a hypothetical mean of zero. This analysis was conducted across the entire sample in order to verify that our task elicited activation within expected regions (e.g., amygdala). Results were thresholded using a two-tailed $p<.05$, corrected for multiple comparisons using AFNI's false discovery rate (FDR) procedure.

An *a priori* region of interest (ROI) analysis was conducted within the bilateral amygdala. ROIs were drawn as spheres with a 5 mm radius centered on Talairach coordinates for the amygdala (x= +/−23, y= 5, z= −15). For each participant, overlap between the bilateral ROI spheres and the right and left amygdala was verified, before calculating the mean BOLD response within the bilateral amygdala. Extracted data thus represented the mean BOLD response within the right and left amygdala during the Observe task relative to rest for each participant. These data served as the dependent variable in subsequent analyses conducted in SPSS (version 20, IBM Corporation).

Neuropsychiatric and Psychosocial Functions

A battery of self-report questionnaires was administered to assess several domains in which HIV+ adults are known to report increased difficulty. Neuropsychiatric symptoms, including current levels of depression, anxiety, and apathy were assessed using the Center for Epidemiological Studies-Depression Scale (CESD) (Radloff 1977), Beck Anxiety Inventory (BAI) (Beck et al. 1988), and the Apathy Evaluation Scale (AES) (Marin et al. 1991), respectively. Alexithymia, which is the inability to identify and describe internal emotions, was assessed with the Toronto Alexithymia Scale (TAS) (Bagby et al. 1994). Psychosocial functions were assessed using the Inventory of Interpersonal Problems (IIP) (Horowitz et al. 2000; Horowitz et al. 1988), which measured the degree of difficulty participants experienced in their interpersonal relationships. All measures were completed within two weeks of the MRI for all participants. On all measures, higher scores indicate greater symptomology.

Because the amygdalae are implicated in a wide diversity of neuropsychiatric and psychosocial functions (e.g., depression, anxiety, interpersonal interactions, social cognition, etc.) (Adolphs 2010; Bickart et al. 2014; Hilbert et al. 2014; Murray et al. 2011; Whalen and Phelps 2009), we sought to capture this diversity of function in a single index. We therefore created a composite score to estimate each participant's global level of functioning across all neuropsychiatric and psychosocial domains assessed. For each participant, z-scores were calculated for each measure based on the mean of the HC group for that measure; the five z-scores were then averaged to create a composite index score for each participant. The index thus represents the overall degree of neuropsychiatric difficulty reported across all domains assessed, with the entire HC group serving as the normative sample. Higher scores on the composite index indicate greater global difficulty relative to HC.

Control Measures

Due to the known impact of current stress and posttraumatic stress disorder (PTSD) on amygdala response (Rosenberger et al. 2009; Shin et al. 2005; van Marle et al. 2009), we assessed the effects of current stress levels and PTSD-related symptomology on amygdala responses in our groups. Levels of current stress and PTSD-related symptoms were quantified using the Perceived Stress Scale (PSS-14) (S. Cohen et al. 1983) and Posttraumatic Checklist - Civilian (PCLC) (Weathers et al. 1993), respectively. We used these measures to assess whether the relation between high ELS and amygdala response was specific, and not confounded by recent stressful life events or subclinical PTSD-related abnormalities in amygdala response.

Prior studies suggest that individual differences in facial emotion recognition abilities are associated with differences in amygdala activation levels (H. Kim et al. 2003; H. Kim et al. 2004). HIV+ adults have been reported to exhibit reduced facial emotion recognition abilities relative to HC adults (Baldonero et al. 2013; Clark et al. 2010a; Clark et al. 2015; Heilman et al. 2013; Lane et al. 2012). Hence, we assessed the effects of facial emotion recognition abilities on amygdala responses in our sample. Facial emotion recognition abilities were assessed utilizing methods employed in prior studies (Circelli et al. 2013; Clark et al. 2010a; Clark et al. 2008, 2010b; Clark et al. 2015). Briefly, participants were

presented with 70 Ekman and Friesen photographs (Ekman & Friesen, 1976) on a 15″ laptop computer. Ten images were displayed in random order from each of the six prototypic emotion categories (Anger, Disgust, Fear, Happy, Sad, Surprise) plus Neutral. For each image, participants indicated which of the seven emotion category labels best described the facial emotion expressed. We examined accuracy rates for angry and fearful facial stimuli only, to maintain correspondence with the affective content of facial stimuli presented in our fMRI paradigm (described above). Accordingly, for each participant, an average emotion recognition accuracy score was derived for angry and fearful faces (Table 1). This accuracy score was used as a covariate in analyses to control for differences in facial emotion recognition abilities. In this way we were able to assess whether HIV-related differences in amygdala response stemmed from HIV-related differences in emotion recognition.

Statistical Analyses

Group differences on demographic variables were assessed using one-way ANOVAs, independent t-tests, and chi-square tests. We verified that the fMRI task elicited significant activation within our bilateral amygdala ROI using a one-sample t-test (versus a hypothetical mean of zero).

The first goal of this study was to examine the independent and combined effects of HIV status and high ELS exposure on levels of amygdala activation. We thus examined the effects of HIV and high ELS on amygdala responses using a two-way ANCOVA with factors of HIV status (HIV, HC) and ELS status (High, Low). Covariates included MR acquisition site (Providence; New York), demographic variables on which the groups differed significantly (i.e., ethnic composition, cocaine use history; Table 1), and control measures described above (current stress [PSS], PTSD symptoms [PCLC], facial emotion recognition abilities). Partial eta-squared (η_p^2) was used as an indicator of effect size, where values of .01, .06, and .14 indicate small, medium, and large effects, respectively (J. Cohen 1988). Next, we conducted a planned comparison to examine the effect of ELS status on amygdala reactivity in the HIV+ group.

Our second goal was to examine whether abnormal amygdala reactivity was associated with elevated neuropsychiatric symptoms in HIV+ adults. First, we determined whether HIV+ adults reported elevated neuropsychiatric symptoms by conducting a two-way ANCOVA with factors of HIV status (HIV, HC) and ELS status (High, Low), which allowed us to examine the effects of both HIV and high ELS on neuropsychiatric and psychosocial functions (composite index). Covariates included demographic variables on which the groups differed significantly (i.e., ethnic composition, cocaine use history; Table 1), as well as current stress levels (PSS), which were included to better control for potential confounding effects of group-related differences in current stress on reported neuropsychiatric symptoms. Next, we conducted a planned pair-wise comparison to examine the effects of ELS status on neuropsychiatric symptoms in the HIV+ group. Cohen's d was calculated as a measure of effect size, where values of 0.2, 0.5, and 0.8 indicate small, medium, and large effects, respectively (J. Cohen 1988). Finally, a linear regression analysis, controlling for MR scanner (Providence; New York), was conducted in the HIV+ group to investigate the relation of amygdala reactivity to neuropsychiatric functions. Mean BOLD

response within the bilateral amygdala was entered into the model as the dependent variable and neuropsychiatric composite index scores served as the independent variable; MR scanner was included in the model as a covariate.

Lastly, linear regression analyses were conducted to examine the relation between amygdala reactivity and key HIV-disease factors known to impact brain function, including nadir CD4 levels, current CD4 levels, current viral load, and length of HIV infection (Chang et al. 2002; Clark and Cohen 2010; R. A. Cohen et al. 2010; Cysique et al. 2006; Heaton et al. 2011). In each model, mean BOLD response within the bilateral amygdala was entered as the dependent variable and the HIV-disease factor of interest was entered as the independent variable; MR scanner was included in each model as a covariate. These analyses allowed us to address mechanistic questions related to our hypothesis that HIV infection is associated with amygdala abnormalities, by assessing whether specific markers of HIV-disease severity (e.g., viral load, current CD4, nadir CD4) were associated with amygdala reactivity levels in HIV+ adults.

Results

Participant Characteristics & Control Measures

Demographic data for the four HIV-ELS groups are reported in Table 1, including group means and statistics. With respect to demographic variables, groups differed significantly in the proportion of Caucasian to non-Caucasian participants and prior cocaine use history (KMSK-C). The HIV+ Low-ELS group reported higher rates of prior cocaine use than HC Low-ELS and HC High-ELS; rates were also higher in HIV+ High-ELS than in HC High-ELS (Table 1). With respect to the control measures, significant group differences were observed in reported levels of current stress, PTSD symptomology, and facial emotion recognition abilities (Table 1). Notably, mean scores on the PTSD symptom scale (PCLC) were below clinically significant levels (<44) for all groups. Demographic differences between the two HIV+ groups were also assessed with respect to HIV-disease variables. HIV + Low-ELS and HIV+ High-ELS groups were well matched with regard to nadir and current CD4 levels, current viral load, and length of HIV infection (Table 1).

fMRI Task of Amygdala Reactivity

The Observe task elicited activation within several neural regions implicated in facial emotion recognition (Fusar-Poli et al. 2009), including the bilateral amygdala and ventral visual stream (Figure 1; Table 2). In addition, deactivation of several regions was also observed, including anterior cingulate cortex (ACC), posterior cingulate, and precuneus, bilaterally (Figure 1; Table 2) – a pattern that is consistent with active suppression of the default mode network (Raichle et al. 2001; Raichle and Snyder 2007).

The Observe task elicited robust activation within the bilateral amygdala ROI across the entire sample, as expected ($t[52]=4.01$, $p<.001$). Results from the two-way ANCOVA ($F[4,48]=3.60$, $p=.01$) controlling for MR scanner revealed that High ELS participants (across both HIV+ and HC groups) demonstrated significantly lower amygdala activation levels than Low ELS participants (main effect of ELS: $F[1,48]=5.70$, $p=.02$, $\eta_p^2=.11$)

(Figure 2). The main effect of HIV and the HIV-ELS interaction were non-significant ($F[1,48]=.79$, $p=.38$, $\eta_p^2=.02$; $F[1,48]=.51$, $p=.48$, $\eta_p^2=.01$, respectively). Ethnicity, cocaine use history, marijuana use status (urine toxicology), current stress levels, PTSD symptomology, and facial emotion recognition abilities did not contribute significantly to the model when entered as covariates (p's >.05) and were thus removed from the analysis. A planned comparison in the HIV+ group controlling for MR scanner indicated that the HIV+ High-ELS group exhibited lower amygdala activation levels than the HIV+ Low-ELS group ($F[1,25]=6.86$, $p=.02$, $\eta_p^2=.22$). Notably, activation levels exhibited by HIV+ High-ELS and HC High-ELS did not differ significantly ($F[1,19]=.01$, $p=.92$, $\eta_p^2<.01$; controlling for MR scanner), which underscores findings from the ANCOVA.

As indicated above, whole-brain voxelwise analyses conducted across the entire sample revealed significant task-related ACC deactivation during the Observe task (Figure 1; Table 2). Because the ACC shares extensive connections with the amygdala (Beckmann et al. 2009; Carmichael and Price 1995; Vogt and Pandya 1987), and is known to modulate amygdala activity in a top-down manner (Etkin et al. 2011), we conducted an explanatory ROI analysis within the ACC. Our goal was to explore whether group differences observed in amygdala activation would also be reflected in the ACC. We created an ROI sphere with a 5 mm radius centered on the Talairach coordinates of this empirically defined region (x= −4, y= −40, z= 14), and calculated the mean BOLD response within this ROI for each participant. Results from the two-way ANCOVA, controlling for MR scanner, were non-significant ($F[4,48]=0.91$, $p=.47$, $\eta_p^2=.07$). While we did observe a tendency for the High ELS groups to exhibit greater ACC deactivation than Low ELS groups, which parallels prior observations of greater default mode network deactivation in adults with high ELS (Philip et al. 2013), this effect was non-significant (main effect of ELS: $F=[1,48]=2.13$, $p=.15$, $\eta_p^2=.04$). Controlling for ethnicity, cocaine use history, current stress levels, PTSD symptomology, facial emotion recognition abilities, or marijuana use status (urine toxicology) did not significantly modify these results.

Neuropsychiatric and Psychosocial Functions

Group mean composite index scores are displayed in Figure 3. Statistical results are listed in Table 3. We conducted a two-way ANCOVA ($p<.001$) to examine the effects of HIV and ELS status on composite index scores, while controlling for the effect of current stress levels (PSS: $p<.001$). Ethnicity, cocaine use history, and marijuana use status (urine toxicology) did not contribute significantly to the model when entered as covariates (p's >.05) and were thus removed from the analysis. Results from the ANCOVA revealed a significant main effect of HIV ($p<.01$), a main effect of ELS that trended toward significance ($p=.07$), and a significant HIV-ELS interaction ($p=.02$). These data indicate that the significant relative increase in the HIV+ groups' neuropsychiatric symptoms was driven by the HIV+ High-ELS group. This is supported by results from the planned pair-wise comparison in the HIV+ group, which revealed that the HIV+ High-ELS group reported significantly higher symptom levels than HIV+ Low-ELS ($t[14.3]=3.24$, $p<.01$, Cohen's $d=1.30$) (Figure 3). By contrast, the increase in mean symptom levels exhibited by HC High-ELS relative to HC Low-ELS was not nearly as large (Figure 3), although group comparisons did indicate a strong trend-level group difference in symptom levels ($t[11.1]=1.86$, $p=.09$, Cohen's $d=.90$).

Follow-up analyses also revealed that the HIV+ High-ELS group reported significantly higher symptom levels than HC High-ELS (t[20]=2.16, p=.04, Cohen's d=.94) as well as HC Low-ELS (t[13.3]=3.79, p<.01, Cohen's d=1.56) (Figure 3).

We conducted explanatory analyses using ANCOVAs, controlling for current stress levels, to examine group differences on each individual neuropsychiatric/psychosocial measure (Table 3). These analyses suggested that the significant main effect of HIV reported above was most strongly driven by HIV+ participants' elevated ratings on measures of depression (p<.01), anxiety (p=.03), and, to a lesser degree, apathy (p=.08, η_p^2=.06) (Table 3). In addition, these explanatory analyses also indicated that the significant HIV-ELS interaction effect observed in the primary analysis was most strongly driven by measures of depression (p=.01), anxiety (p=.04), and alexithymia (p=.05) (Table 3). Follow-up analyses confirmed that, relative to HIV+ Low-ELS participants, HIV+ High ELS participants reported significantly higher levels of depression (t[16.8]=3.74, p<.01, Cohen's d=1.48), anxiety (t[13.1]=2.27, p=.04, Cohen's d=.92), apathy (t[25]=2.08, p=.05, Cohen's d=.80), and alexithymia (t[26]=3.03, p<.01, Cohen's d=1.15). For descriptive purposes, we report group mean scores for each of these measures in Table 4.

Relation of Amygdala Reactivity to Neuropsychiatric and Psychosocial Functions in HIV+ Adults

Results from the linear regression analysis are reported in Table 5. In the HIV+ group there was a significant association between amygdala activation and composite index scores, where lower activation was associated with higher reported neuropsychiatric symptoms (p=.01) (Figure 4). We conducted explanatory analyses to examine specific associations between amygdala reactivity and individual neuropsychiatric/psychosocial domains. Restricting these analyses to domains in which significant group differences were observed (depression, anxiety, apathy, alexithymia), we found that lower amygdala activation levels correlated significantly with higher levels of depression (p=.05), anxiety (p=.03), and alexithymia (p=.01) in HIV+ (Table 5).

Relation of Amygdala Reactivity to HIV-Disease Factors

The relation between HIV-disease factors (nadir CD4, current CD4 levels, current viral load, length of HIV infection) and amygdala activation in the HIV+ group were examined using linear regression. A significant association between nadir CD4 levels and amygdala activation was observed, where lower nadir CD4 counts (i.e., poorer historical immunological health) were associated with higher activation levels (R^2=.48; F[2,26]=11.07, p<.01; β=−.46, [t=−2.88, p<.01]). No additional significant associations were observed.

Discussion

This study investigated whether HIV+ adults exhibit abnormal levels of amygdala activation, and assessed whether these abnormalities were associated with higher levels of neuropsychiatric symptoms. We examined the impact of HIV infection and high ELS on amygdala activation levels in our HIV+ sample based on the evidence that high ELS exposure is linked to abnormal amygdala activity in non-HIV cohorts (Dannlowski et al.

2012; Evans et al. 2015; Grant et al. 2011; Taylor et al. 2006) and abnormal amygdala morphometry in HIV+ adults (Clark et al. 2012). Briefly, we found that high ELS status was associated with reduced levels of amygdala activation. In addition, HIV+ adults with high ELS reported higher levels of neuropsychiatric symptoms relative to HIV+ adults with low ELS and healthy control adults. Lastly, we found that reduced levels of amygdala activation were associated with higher levels of neuropsychiatric symptoms in HIV+ adults. To our knowledge, this is the first evidence linking aberrant amygdala activity to elevated neuropsychiatric symptoms in HIV+ adults. Collectively, our results suggest that, for HIV+ adults, having a history of high ELS exposure is a significant risk factor for experiencing neuropsychiatric symptoms in adulthood. In addition, our findings implicate ELS-related abnormalities in amygdala activity in the etiology of neuropsychiatric symptoms in HIV+ adults.

ELS-related abnormalities in amygdala activity have been observed previously in non-HIV samples, though findings have varied. Studies have reported increased (Dannlowski et al. 2012; Evans et al. 2015; Grant et al. 2011), as well as decreased (Taylor et al. 2006) amygdala activation in non-HIV adult samples with high ELS. It is notable that ELS-related reductions in amygdala activity, as reported here and elsewhere (Taylor et al. 2006), are exclusive to studies that examine amygdala responses relative to a resting baseline (as opposed to an active baseline). There is some evidence that absolute blood flow in the amygdala at rest correlates positively with stress exposure (Canli et al. 2006). Hence, it is possible that reduced amygdala responses observed in our high ELS participants may reflect hyperactive baseline levels of amygdala activity, which create a ceiling effect, whereas participants with low ELS may be more able to generate increases in amygdala activation in response to threat stimuli. This suggestion is consistent with a number of studies documenting reduced amygdala responses to threat stimuli, and elevated baseline amygdala activity at rest in adults with high stress exposure, depression, or other related disorders (Canli et al. 2005; Drevets 1999; Drevets et al. 2002; Heinz et al. 2007; Lanius et al. 2010; Payer et al. 2012; Seeley et al. 2007; Sripada et al. 2012; Taylor et al. 2006). Thus, while reduced amygdala activation in high ELS adults may at first appear unexpected, the observed finding does in fact fit within the broader framework of the literature. Yet, it is also possible that reduced amygdala responses observed in our high ELS participants could reflect ELS-related abnormalities within regions known to modulate amygdala function (e.g., ACC, ventromedial prefrontal cortex). While our explanatory ROI analyses in the pregenual ACC did not reveal significant group-related effects, future investigations that focus on these regions will help to clarify this issue.

We found strong evidence that high ELS exposure was associated with elevated neuropsychiatric symptoms in HIV+ adults. Our data align with prior studies that have reported elevated depression and anxiety levels in HIV+ adults with a history of physical and/or sexual abuse (Mimiaga et al. 2009; Schafer et al. 2013; Simoni and Ng 2000; Spies et al. 2012; Welles et al. 2009). Notably, there has been little examination of the long-term mental health effects of other forms of childhood maltreatment, beyond physical and sexual abuse, in HIV+ adults (Spies et al. 2012). Investigation of a wider range of adverse childhood experiences (ACEs) is critical, as some ACEs, particularly poverty and neglect, persist at high rates in many societies, including the US (DeNavas-Walt and Proctor 2015;

Gilbert et al. 2009). Our study thus adds to the prior literature by assessing exposure to a number of ACEs (e.g., physical abuse, sexual abuse, poverty, neglect), and by linking cumulative ACE exposure (i.e., high ELS) to a number of neuropsychiatric symptoms commonly endorsed by HIV+ adults (depression, anxiety, apathy, alexithymia). This result represents a novel finding in HIV+ cohorts, and parallels studies implicating high ELS as a significant risk factor for elevated neuropsychiatric symptoms in non-HIV samples (Dube et al. 2003; Felitti et al. 1998; Kaufman and Charney 2001; McFarlane et al. 2005; Pechtel and Pizzagalli 2011; Pesonen and Raikkonen 2012; Repetti et al. 2002; Taylor 2010).

We observed a strong association between elevated neuropsychiatric symptoms and aberrant amygdala responses in HIV+ patients. This effect was observed across a broad range of neuropsychiatric domains, and most notably for ratings of depression, anxiety, and alexithymia. Interestingly, we did not find a strong association between amygdala responses and apathy ratings, despite greater reports of apathy symptoms in the HIV+ group, which is in line with prior data indicating that the neural correlates of apathy and depression in HIV+ adults are distinct (Paul et al. 2005). The overall picture that emerges, however, is consistent with the larger literature documenting the importance of the amygdala to neuropsychiatric symptomology in non-HIV samples (Hilbert et al. 2014; Murray et al. 2011; Whalen and Phelps 2009). Additional studies would be needed to determine whether the association between ELS-related abnormalities in amygdala response and neuropsychiatric symptoms in HIV+ adults differs from that observed in HC adults presenting with a similar range of neuropsychiatric symptoms. Nevertheless, in the current study it is notable that while both the HIV+ High-ELS and HC High-ELS groups exhibited similar levels of amygdala responses, reported levels of neuropsychiatric symptoms were considerably higher in the HIV+ High-ELS group. This observation suggests that HIV-related abnormalities may be occurring in additional neural regions that may act in concert with ELS-related effects in the amygdala to elevate neuropsychiatric symptoms in HIV+ High-ELS adults. For example, in non-HIV cohorts, elevated neuropsychiatric symptoms have been associated with abnormalities within a number of regions, including the subgenual ACC (Damsa et al. 2009; Holzschneider and Mulert 2011; Mayberg 1997; Price and Drevets 2012), which is affected by HIV (Clark et al. 2015; Kuper et al. 2011). Future studies that examine potential additive effects of HIV-related and ELS-related abnormalities across a larger number of neural regions will provide a more comprehensive understanding of these networks and their relation to neuropsychiatric symptoms in HIV+ adults with high ELS.

Results from this study hint at the possibility that HIV infection and high ELS have independent effects on amygdala activity. Whereas high ELS status was associated with lower amygdala response, in contrast, greater historical immunological suppression in HIV+ patients (lower nadir CD4 levels) was associated with higher amygdala response. This finding suggests that severity of immunosuppression can exert a legacy effect on amygdala functions in HIV+ adults, consistent with several studies linking lower nadir CD4 levels to greater degree of neural abnormality in HIV+ adults (Clark et al. 2012; Clark et al. 2015; R. A. Cohen et al. 2010; Hua et al. 2013; Jernigan et al. 2011). HIV-related neural abnormalities include marked differences in frontal-lobe function (Castelo et al. 2006; Melrose et al. 2008). Accordingly, it is possible that the association between greater amygdala reactivity and lower nadir CD4 levels might be driven by HIV-related effects in

frontal-lobe regions responsible for modulating amygdala response (M. J. Kim et al. 2011). Although we did not observe HIV-related differences in amygdala activation that were associated with neuropsychiatric symptoms, neuropsychiatric dysfunction in HIV+ adults is known to be multifactorial (Hammoud et al. 2010; Paul et al. 2005; Smith et al. 2008; Stubbe-Drager et al. 2012). It is likely that the neural mechanisms underlying neuropsychiatric dysfunction in HIV+ adults differ with respect to the different etiological factors involved (acute symptomatic illness, high ELS, etc.). Continued investigation of HIV-specific neural abnormalities is needed in order to advance individually-tailored prevention and intervention strategies for neuropsychiatric disorders in HIV+ adults.

Findings from this study have important clinical implications. First, our results suggest that assessing ELS histories in HIV+ patients could potentially enhance early identification of those at risk for developing neuropsychiatric symptoms. According to our data, HIV+ adults with high ELS exposure may be more likely to experience neuropsychiatric symptoms. These findings, coupled with those from similar studies (Mimiaga et al. 2009; Simoni and Ng 2000; Welles et al. 2009), have the potential to inform current conceptualizations of neuropsychiatric disorders in HIV+ patients (e.g., Rabkin 2008). Collectively, these studies suggest that high ELS exposure should be placed among other known risk factors of neuropsychiatric symptoms in HIV+ patients (e.g., acute symptomatic illness, stigma, substance abuse, social isolation). Second, the finding that the HIV+ High-ELS group exhibited significant elevations in neuropsychiatric symptoms relative to all other groups suggests that there might be a benefit in tailoring treatment approaches specifically to this group. At present, empirically supported interventions for HIV+ adults with high ELS exposure are scarce (Seedat 2012). Studies conducted in non-HIV samples indicate that psychotherapy is a critical component of successful symptom reduction for high ELS adults diagnosed with depression, even more so than pharmacotherapy alone (Blalock et al. 2013; Nemeroff et al. 2003; Zobel et al. 2011). Hence, treatment approaches that involve a psychotherapeutic component might be particularly effective for HIV+ High-ELS patients and thus warrant further examination. Third, our data suggest that ELS-related mechanisms (e.g., Carpenter et al. 2010a; Carpenter et al. 2010b; Irwin and Cole 2011; Johnson et al. 2013; Taylor 2010; Tyrka et al. 2013) might provide valuable targets for intervention when developing therapeutic strategies for neuropsychiatric disorders in HIV+ adults with high ELS. Accordingly, future studies are needed to determine whether biological mechanisms linked to high ELS exposure (e.g., increased cytokines) (Carpenter et al. 2010a; Tyrka et al. 2013) are associated with neural abnormalities in HIV+ adults with high ELS, as such studies may help to identify potential targets for intervention.

Some limitations of this preliminary study and considerations for future work include the following. First, our sample size was small, thereby limiting statistical power. However, we maximized power by using an ROI approach in our fMRI analysis and restricted our main analysis to one neural region (bilateral amygdala). Second, this study utilized retrospective reports of ELS history, which may be prone to report bias, revisionist recall error, and normal forgetting (Hardt and Rutter 2004; Maughan and Rutter 1997). It is notable that studies which utilize retrospective assessments of ELS and those that utilize objective documentation of ELS exposure (e.g., governmental records) find similar effects on neural, behavioral, and health outcomes (Clark et al. 2012; Felitti et al. 1998; Mehta et al. 2009;

Pesonen and Raikkonen 2012; Tottenham et al. 2009a). Such findings support the notion that retrospective assays of ELS history provide data that have strong biological relevance. Third, in creating the neuropsychiatric composite index scores we utilized the entire HC group, rather than the HC Low-ELS group, as the normative sample. Using this approach, the resulting z-scores underestimate the relative level of symptomology reported by our High-ELS groups, thus dampening the magnitude of our ELS-related effects. Yet, using the entire HC group as the normative sample allows us to depict the degree to which our two HIV+ groups deviate from the larger random sample of demographically-matched HC adults. This approach thus increases the generalizability of our data. Additionally, the overall pattern of results reported herein remains the same whether the entire HC group or the HC Low-ELS group is used as the normative sample. Fourth, our groups differed significantly with respect to history of remote cocaine use. Although our analyses indicated that group differences in remote cocaine use did not contribute significantly to the observed effects, it remains possible that group differences in cocaine use history may have an indirect influence on our findings. Future studies should investigate the brain effects of HIV and ELS in samples in which remote substance use histories are more systematically controlled.

In summary, we observed evidence that high ELS exposure is a significant risk factor for elevated neuropsychiatric symptoms in HIV+ adults. This observation should guide future investigations of the neural etiology of neuropsychiatric disorders in HIV+ samples. Our data serve as an important first step in this direction, as they reveal ELS-related neural correlates of neuropsychiatric symptoms in HIV+ adults. More specifically, we found that in HIV+ adults, high ELS exposure is associated with altered amygdala response, which correlates with elevated neuropsychiatric symptoms. Future studies should be conducted to examine additional HIV-related and ELS-related brain effects that might play a role in the development of neuropsychiatric symptoms in HIV+ adults. In addition, future studies with larger sample sizes will help to confirm whether HIV and high ELS do indeed have independent effects as suggested here, or whether they might also have additive biological effects on amygdala function [e.g., through their impact on the immune system (Boyce et al. 1995; Glaser et al. 1986; Leserman 2003, 2008; Miller et al. 2002; Zachariae 2009)]. Collectively, such studies have the potential to improve diagnostic and treatment strategies for neuropsychiatric disorders in HIV+ adults by identifying potential biomarkers (e.g., neural signatures, cytokines) that could enhance early detection of HIV+ adults at risk of developing neuropsychiatric disorders, and by identifying specific targets for therapeutic intervention.

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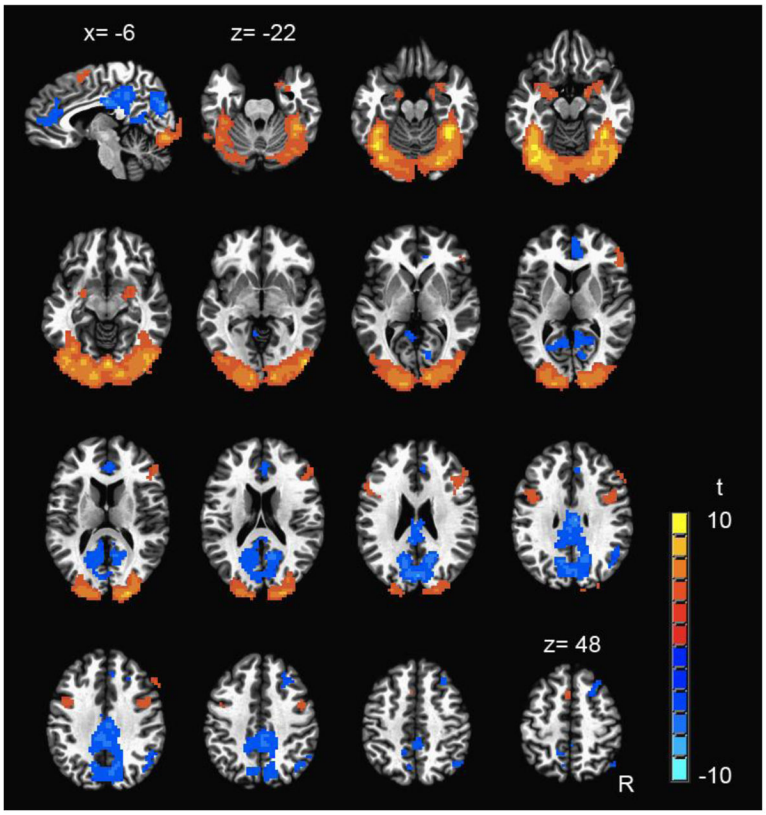

Figure 1.

Regions of significant response during the Observe task (p<.05, FDR corrected) across the entire sample (N=53). One sagittal image (upper left) and 15 axial images are shown. For the sagittal image, x = −6. Axial images begin at z = −22 and increase in 5 mm increments. R = right.

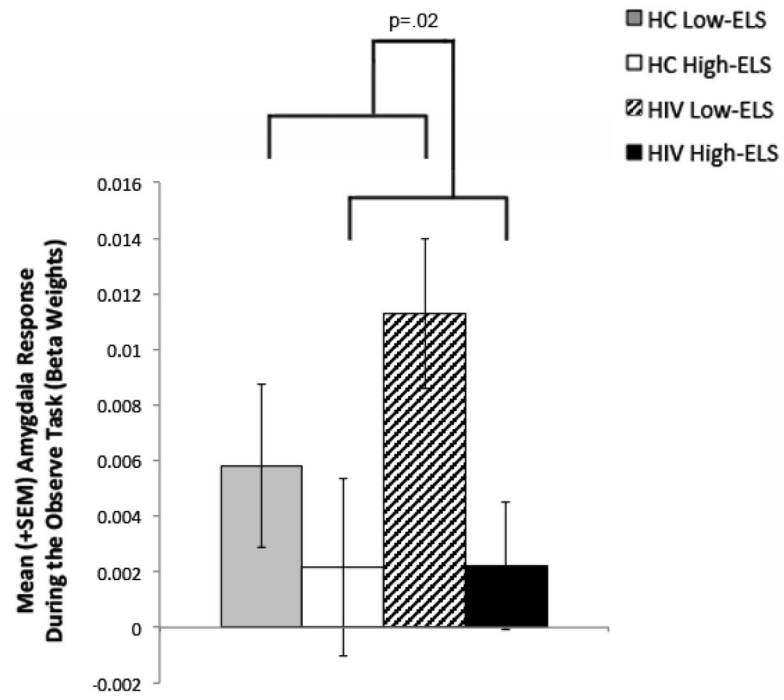

Figure 2.

High ELS status is associated with reduced BOLD response in the bilateral amygdala during observation of angry/fearful faces (versus rest). ELS = early life stress; BOLD = blood oxygen level dependent; SEM = standard error of the mean; HC = HIV-negative Control.

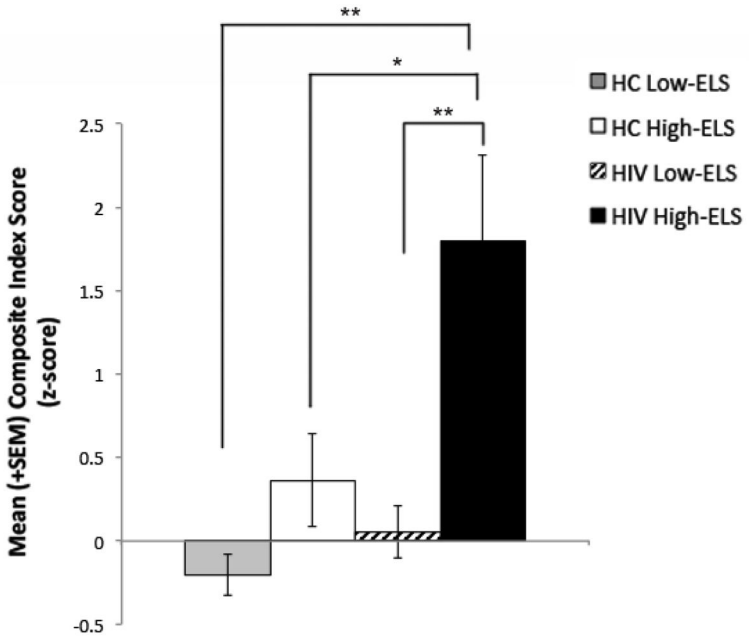

Figure 3.

HIV+ High-ELS participants report greater levels of neuropsychiatric/psychosocial difficulty (composite index score) than all other groups. SEM = standard error of the mean; HC = HIV-negative Control; ELS = early life stress. *p<.05, **p<.01.

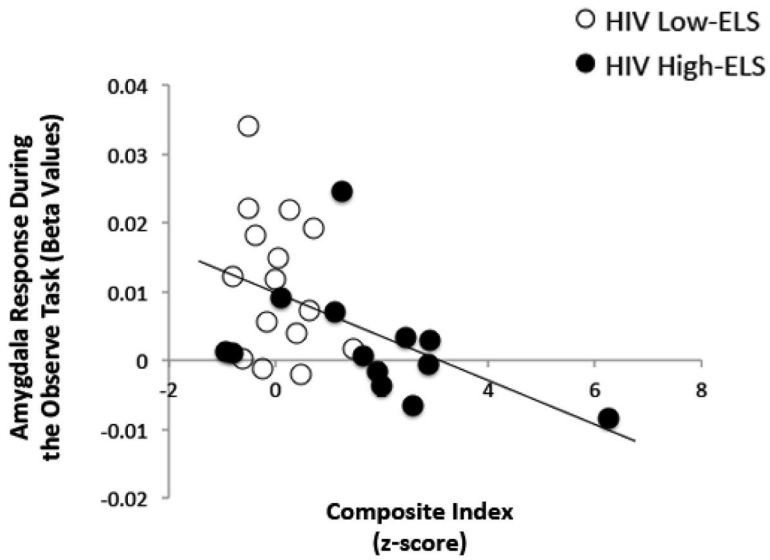

Figure 4.

Lower BOLD response in the bilateral amygdala is associated with greater neuropsychiatric and psychosocial difficulties (composite index) in HIV+ participants. BOLD = blood oxygen level dependent; ELS = early life stress.

Table 1

Demographic Characteristics of the Participant Groups

	HC Low-ELS (N=16)		HC High-ELS (N=9)		HIV+ Low-ELS (N=15)		HIV+ High-ELS (N=13)				
Variable	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***F/t/χ^2***	***df***	***p***
Recruitment Site (% Providence, RI)	68.8		55.6		53.3		61.5		0.88	3	0.832
% New York, NY	31.3		44.4		46.7		38.5				
Age (years)	46.8	13.1	48.6	12.3	46.3	8.9	49.0	10.2	0.18	3,49	0.907
% Male	56.3		77.8		60.0		53.8		1.49	3	0.686
Mini-Mental Status Exam (/30)	28.8	1.3	28.8	1.0	29.1	0.9	28.0	1.7	1.94	3,49	0.136
Ethnic composition (% Caucasian)	43.8		77.8		20.0		38.5		7.82	3	0.050
% African American	50.0		11.1		80.0		53.8				
% Native American							7.7				
% Biracial or “Other”	6.3		11.1								
% Hepatitis C positive	6.3		11.1		33.3		23.1		4.22	3	0.239
KMSK – Alcohol (/13)	6.1	3.4	8.1	3.4	7.5	3.4	6.5	3.7	0.84	3,49	0.480
KMSK – Cocaine (/16)	3.1^{a}	5.6	$1.3^{b,c}$	3.6	$7.5^{a,b}$	6.7	7.4^{c}	6.3	3.32	3,49	0.027
KMSK – Opiate (/13)	0.6	1.8	0.2	0.7	2.7	4.6	1.0	2.3	2.03	3,49	0.121
% With positive marijuana toxicology	6.3		0.0		13.3		23.1		4.25	3	0.235
Nadir CD4 (cells/μl)					244.5	258.8	290.7	262.0	0.46	25	0.651
Current CD4 (cells/μl)					677.9	399.0	741.9	354.2	0.45	26	0.659
Current log10 viral load (copies/ml)					2.4	1.3	2.2	1.1	0.48	26	0.634
Length of HIV infection (years)					17.1	6.6	18.3	7.0	0.48	26	0.635
% On ARV medications					100.0		92.3				0.464
Number of ELS events	$1.0^{a,b}$	0.8	$5.0^{a,c}$	2.7	$1.4^{c,d}$	0.7	$5.3^{b,d}$	2.1	25.47	3,49	<0.001
Current stress – PSS (/70)	12.4^{a}	7.3	20.1	8.0	13.7	6.5	22.5^{a}	10.2	5.13	3,49	0.004
PTSD symptoms – PCLC (/85)	20.4^{a}	3.9	23.3^{b}	11.4	24.1^{c}	10.4	$38.6^{a,b,c}$	16.7	7.11	3,49	<0.001
Anger & Fear facial emotion recognition (% correct)	$76.9^{a,b}$	15.7	71.4	8.8	59.7^{a}	13.6	55.0^{b}	24.5	5.01	3,49	0.004

Note: HC = HIV-negative Control; KMSK = Kreek-McHugh-Schluger-Kellogg scale; ARV = antiretroviral; ELS = early life stress; PSS = Perceived Stress Scale; PTSD = Posttraumatic stress disorder; PCLC = Posttraumatic Checklist - Civilian. Across rows, means with the same superscript are significantly different at the $p<.05$ level.

Table 2

Regions of Significant Response to the Observe Task Across the Entire Sample (N=53)

Region	BA	Coordinates (x, y, z)	Cluster size (voxels)	*t*-score	*p*-value
L/R Lingual Gyrus/Fusiform Gyrus	17, 18, 19, 37	−1, 80, −4	3718	5.0512	<0.0001
L/R Posterior Cingulate/Precuneus	7, 23, 31	−1, 59, 27	1420	−4.2261	0.0001
R Inferior/Middle Frontal Gyrus	6, 9, 45, 46	−47, −21, 22	212	3.7373	0.0005
R Amygdala and Parahippocampal Gyrus	28, 34	−26, 1, −17	137	3.8691	0.0003
L/R Anterior Cingulate Cortex	10, 24, 32	−4, −40, 14	112	−3.6712	0.0006
R Superior/Middle Frontal Gyrus	6, 8	−27, −23, 46	92	−3.5670	0.0008
R Angular Gyrus	39	−45, 59, 37	81	−3.5170	0.0009
L Inferior/Middle Frontal Gyrus	6, 9	43, −7, 28	78	3.4961	0.0010
L Amygdala	34	22, 3, −11	68	3.9859	0.0002
L/R Medial Frontal Gyrus	6	1, −5, 54	67	3.7423	0.0005

Note: Central voxel coordinates are listed using the Talairach and Tournoux atlas. BA = Brodmann area(s); L = left; R = right.

Table 3

Group Comparisons of Neuropsychiatric and Psychosocial Measures

	Omnibus				Main Effect of HIV				Main Effect of ELS				HIVxELS Interaction			
Neuropsychiatric/Psychosocial Domain	***F***	***df***	***p***	η_p^2	***F***	***df***	***p***	η_p^2	***F***	***df***	***p***	η_p^2	***F***	***df***	***p***	η_p^2
Composite Index (z-score)	18.86	4,48	<.001	.61	7.74	1,48	<.01	.14	3.57	1,48	.07	.07	5.70	1,48	.02	.11
Depression (CESD)	24.47	4,48	<.001	.67	11.11	1,48	<.01	.19	6.66	1,48	.01	.12	6.59	1,48	.01	.12
Anxiety (BAI)	7.29	4,48	<.001	.38	4.98	1,48	.03	.09	0.85	1,48	.36	.02	4.34	1,48	.04	.08
Apathy (AES)	5.41	4,47	.001	.31	3.15	1,47	.08	.06	0.79	1,47	.38	.02	0.07	1,47	.80	.00
Alexithymia (TAS)	7.45	4,48	<.001	.38	0.59	1,48	.45	.01	0.92	1,48	.34	.02	4.06	1,48	.05	.08
Interpersonal Problems (IIP)	2.26	4,47	.076	.16	0.00	1,47	.96	.00	0.44	1,47	.51	.01	0.50	1,47	.48	.01

Note: The Composite Index represents the overall degree of neuropsychiatric difficulty reported across all domains assessed, with the HC group serving as the normative sample. CESD = Center for Epidemiological Studies-Depression Scale; BAI = Beck Anxiety Inventory; AES = Apathy Evaluation Scale; TAS = Toronto Alexithymia Scale; IIP = Inventory of Interpersonal Problems. All analyses control for current stress levels, as reported on the Perceived Stress Scale.

Table 4

Group Mean Scores on Neuropsychiatric and Psychosocial Measures

	HC Low-ELS		HC High-ELS		HIV+ Low-ELS		HIV+ High-ELS	
Neuropsychiatric/Psychosocial Domain	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***	***Mean***	***SD***
Composite Index (z-score)	−0.20	0.49	0.36	0.84	0.06	0.61	1.80	1.85
Depression (CESD)	3.00	3.52	8.56	7.04	5.67	6.34	20.54	13.07
Anxiety (BAI)	0.94	1.84	1.67	2.55	1.80	2.57	9.15	11.43
Apathy (AES)	23.56	4.76	26.78	7.65	26.21	4.46	30.46	6.08
Alexithymia (TAS)	37.94	8.81	40.33	11.02	35.80	9.82	49.54	14.06
Interpersonal Problems (IIP)	47.50	34.70	76.67	47.10	58.57	38.83	73.00	50.21

Note: The Composite Index represents the overall degree of neuropsychiatric difficulty reported across all domains assessed, with the HC group serving as the normative sample. The Composite Index is expressed as a z-score, whereas means for all other measures represent mean raw scores. Higher scores on all measures, including the Composite Index, indicate greater global difficulty. ELS = early life stress; HC = HIV-negative Control; CESD = Center for Epidemiological Studies-Depression Scale; BAI = Beck Anxiety Inventory; AES = Apathy Evaluation Scale; TAS = Toronto Alexithymia Scale; IIP = Inventory of Interpersonal Problems.

Table 5

Associations Between Amygdala BOLD Responses and Neuropsychiatric Measures in Each Group

	HC Group							HIV+ Group						
	Model Statistics				*Predictor*			*Model Statistics*				*Predictor*		
Neuropsychiatric/Psychosocial Domain	**R^2**	**F**	**df**	**p**	**β**	**t**	**p**	**R^2**	**F**	**df**	**p**	**β**	**t**	**p**
Composite Index	.03	.31	2,24	.74	−.06	−0.29	.78	.44	9.70	2,27	<.01	−.44	−2.90	.01
Depression (CESD)	.02	.27	2,24	.77	−.01	−0.03	.98	.35	6.84	2,27	<.01	−.33	−2.03	.05
Anxiety (BAI)	.03	.28	2,24	.76	−.03	−0.14	.89	.38	7.71	2,27	<.01	−.37	−2.33	.03
Apathy (AES)	.04	.43	2,24	.65	−.12	−0.57	.58	.29	4.79	2,26	.02	−.21	−1.13	.27
Alexithymia (TAS)	.06	.70	2,24	.51	.19	0.92	.37	.45	10.05	2,27	<.01	−.45	−2.99	.01
Interpersonal Problems (IIP)	.08	.96	2,24	.39	−.24	−1.17	.25	.34	6.22	2,26	.01	−.31	−1.85	.08

Note: These data summarize results from linear regression analyses conducted in each group. Each model assesses the relation between bilateral amygdala response and a single neuropsychiatric domain (predictor) controlling for MR acquisition site. The Composite Index is a measure of the overall degree of neuropsychiatric difficulty reported across all domains assessed. BOLD = blood oxygen level dependent; HC = HIV-negative Control; CESD = Center for Epidemiological Studies-Depression Scale; BAI = Beck Anxiety Inventory; AES = Apathy Evaluation Scale; TAS = Toronto Alexithymia Scale; IIP = Inventory of Interpersonal Problems.