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HIV and Early Life Stress on Neuroimaging and Risky Behavior

Paola Garcia Egan
University of Missouri-St. Louis, pmgb7b@mail.umsl.edu

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by

Paola M. García Egan

M.A. in Psychology, May, 2017, University of Missouri-St. Louis
M.S. in Psychology, April, 2009, University of Hamburg
B.A. in Psychology, July, 2006, University of Hamburg

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Advisory Committee

Robert Paul, Ph.D. ABPP-CN
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Sandra Langeslag, Ph.D.
Committee Member

Jodi Heaps-Woodruff, Ph.D.
Committee Member

Beau Ances, MD. Ph.D. MS.
Committee Member

Abstract

This study examined the interactive effects of early life stress (ELS) and HIV on brain morphometry, diffusion-basis-spectrum-imaging (DBSI), risky decision-making, and sex-risk behavior. 122 people with HIV (PWH) and 113 people without HIV (PWoH), free of major psychiatric illness and neurological confounds, were stratified into high (≥ 3 events) vs. low (< 3 events) ELS [PWoH/low ELS (n = 57), PWoH/high ELS (n =56), PWH/low ELS (n = 43), PWH/high ELS (n = 79)] and underwent structural magnetic resonance imaging, DBSI, neuropsychological, and risky-behavior assessment; all PWH were virologically controlled. Compared to PWoH, PWH had smaller orbitofrontal cortex (OFC), parietal lobes, insula, caudate and anterior cingulate. No ELS effects were detected in volumetric measures. Significant interactions were found between HIV serostatus and ELS on the OFC and on cellularity of the inferior fronto-occipital fasciculus after multiple comparisons adjustment. Specifically, PWH/high ELS exhibited significantly smaller OFC and PWoH/high ELS show significantly larger OFC than the other groups. PWoH/high ELS exhibited higher DBSI cellularity (neuroinflammation proxy) of the inferior-occipital-fasciculus compared to PWoH/high ELS. Regardless of HIV status, executive function moderated the relationship between the OFC and sex-risk behavior such that individuals within the sample who performed above average on a measure of executive function and had a larger OFC reported fewer sex partners in past six months than individuals with smaller volumes. No interaction was found between HIV serostatus and ELS on risky behavior measures. Clustering analyses defined ELS subgroups in PWH that were determined by demographic characteristics, duration of infection, recent CD4+ T-cell count, nadir CD4+ T-cell count and high/low ELS. Even in

PWH that are virologically controlled, without major current psychiatric comorbidities, there is evidence of a synergistic impact of ELS and HIV on OFC volumes. Higher volumes in the OFC were detrimental when associated with lower executive function scores or advantageous when associated with higher executive function. Findings suggest that ELS is associated with different brain signatures among PWoH and virally suppressed PWH. However, ELS was not directly associated with risky behaviors, and subgroups in PWH were characterized by demographic variables, past substance use and HIV clinical variables.

HIV and Early Life Stress on Neuroimaging and Risky Behavior

Human immunodeficiency virus (HIV) represents one of the greatest health challenges of modern time. Despite intense efforts to eradicate the disease, more than 38 million adults are currently living with HIV worldwide, with approximately 1.7 million new cases reported in 2019 (HIV.gov, 2021). In the US, the incidence of HIV has declined since the peak in the mid-1980s. Unfortunately, financial and environmental stressors such as reduced access to healthcare resources and preventive programs have left some marginalized groups showing increased rates of infection and decreased rates of viral suppression. Antiretroviral treatment (ART) is highly effective at controlling HIV replication (Davenport et al., 2019; Günthard et al., 2016). However, only half of people with HIV (PWH) in the US receive ART, and only 70% of those who initiate treatment achieve viral suppression below limits of detection due to poor adherence (CDC, 2020b). These statistics are far below the targets established by the United Nations AIDS to ensure that 95% of the seropositive population are receiving ART and 95% of those individuals achieve viral suppression (UNAIDS, 2021). Suboptimal HIV treatment and patient care experienced by marginalized groups of individuals in the US result in a high burden of HIV-related health complications and HIV-associated health comorbidities, including brain dysfunction (for review see Paul, 2019).

Multifactorial Etiology of Brain Disruption in HIV

HIV crosses the blood-brain barrier and reaches the brain within eight days of infection (Valcour et al., 2012; Veenstra et al., 2017). A cascade of neuroinflammatory events take place in early HIV infection, characterized by an influx of lymphocytes and monocytes into the central nervous system (CNS; Navia et al., 1986; Price et al., 1988)

and release of neurotoxic cytokines such as tumor-necrosis factor-α and interleukin 1-ß in the CNS (Kaul et al., 2001; Valcour et al., 2012). Both systemic immune activation and neurotoxins released due to presence of the virus can damage neurons through diverse mechanisms, including programed cell death of infected glia cells (Doitsh et al., 2014), apoptosis of uninfected bystander cells, and direct CD4+ T-cell cytotoxicity inducing apoptosis of target cells (Garg et al., 2012). Additionally, the virus causes neuronal loss through neurotoxins (e.g., glycoprotein gp120 and HIV trans-activator) secreted by infected cells in the CNS (Magnuson et al., 1995).

Chronic neuroHIV symptoms are associated with ongoing disease mechanisms after the onset of ART. Despite viral suppression, recent studies show that brain reservoirs in PWH contain macrophages and microglia harboring HIV DNA (Ko et al., 2019), which are thought to induce chronic immune activation (Imp et al., 2017; Oliveira et al., 2017). Furthermore, a post-mortem study of virally suppressed individuals identified increased levels of microglial/macrophage cells in the hippocampus and basal ganglia compared to people without HIV (PWoH; Anthony et al., 2005). However, new research indicates that chronic HIV can also be sustained by monocytes migrating into the CNS (Joseph et al., 2019). These studies suggest a vicious cycle in which HIV-infected cells persist, despite ART, and perpetuate inflammation that ultimately damages neuronal support cells and alters neuronal activity.

Cognitive Impairments And Brain Abnormalities Are Common in PWH

HIV adversely affects cognitive domains involving attention/working memory, processing speed, executive functioning, verbal learning, and motor speed, with relative sparing of core language and memory consolidation networks (Antinori et al., 2007;

Brouillette et al., 2016; Gawron et al., 2019). Effective ART treatment has reduced the severity, but not the pervasiveness of these impairments, with cognitive difficulties affecting approximately 50% of PWH, even among virally suppressed individuals (Gott et al., 2017; Rubin et al., 2017; Cysique & Becker, 2017). A recent machine learning study of PWH on ART revealed different phenotypes with mild to moderate cognitive difficulties (Paul et al., 2022). The severity of cognitive complications have potential to interfere with daily living skills such as driving ability, work performance (Cross et al., 2013; Woods et al., 2008; Delle Donne et al., 2020; Gouse et al., 2021), and adherence to ART (Thaler et al., 2015; Cooley et al., 2020; Nweke et al., 2022). Further, studies indicate higher risk-taking behavior, such as substance use and unprotected sex, among PWH who exhibit cognitive impairment (Anand et al., 2010; Anderson et al., 2016). This is important considering that risk-taking behavior is associated with HIV transmission and poor adherence to HIV treatment (Hernández Huerta et al., 2016; Kalichman, 2003; Kalichman et al., 2010; Mellins et al., 2011; Ndziessi et al., 2012).

HIV-related cognitive impairment corresponds with neuroimaging abnormalities involving cortical-subcortical networks (Guha, Brier, et al., 2016; Nichols et al., 2018; Righart et al., 2013; Tekin & Cummings, 2002; Vik et al., 2015; Ipser et al., 2015; Luckett et al., 2021). PWH on ART exhibit subcortical volume loss in the caudate, putamen, nucleus accumbens, globus pallidus, and thalamus (Ances et al., 2012; Clifford et al., 2017; Kallianpur et al., 2019; O'Halloran et al., 2019; Ortega et al., 2013; Sanford et al., 2017; Tesic et al., 2018). Reduced white matter volumes in frontal, parietal, brainstem, and thalamic areas have been reported in virally suppressed PWH (Nichols et al., 2019; Chang et al., 2020), which might reflect legacy effects of early infection,

inflammation related to toxicity of ART and/or the presence of comorbidities such as cardiovascular disease. For example, a higher burden of white matter intensities in PWH is associated with longer duration of immune suppression (e.g., CD4+ T-cell count below 500 cells/mm^3), older age, and cardiovascular risk factors (Su et al., 2016; Sanford et al., 2019; Murray et al., 2021). Furthermore, studies report reduced microstructural integrity of the corpus callosum (van Zoest et al., 2018; Chang et al., 2020; Paul et al., 2021) and diffuse cerebral cellularity (a neuroinflammatory marker) in virologically well-controlled PWH compared to PWoH (Strain et al., 2017). These studies suggest that neuroinflammation, reduced white matter integrity, and reduced gray and white matter volumes endure after the initiation of ART contributing to neuroimaging alterations seen in PWH.

While the virus does not infect neurons per se, network alterations in both cortical and subcortical regions are believed to occur in relation to regional and brain-wide network disruptions (L. M. Baker et al., 2017; Liu et al., 2022). One mechanism behind these network disruptions, as well as brain structural changes, is hypothesized to be the result of increased inflammation leading to neuronal death. Examples of cortical alterations in PWH include cortical thinning and regional volume loss throughougt the brain, including the cerebellum, even when reaching viral suppression (Clifford et al., 2017; Sanford et al., 2019; Cooley et al., 2021; Nir et al., 2021; Nichols et al., 2019; Cole et al., 2018), affecting both cognitive and motor functioning (Sanford et al., 2019; Cooley et al., 2021; Clifford et al., 2017; Nichols et al., 2019).

Studies show that PWH who have low level viremia (20–200 copies/mL) exhibit lower functional connectivity in diverse areas including frontal and parietal areas,

caudate, visual cortex, cerebellum, salience and frontoparietal networks compared to PWoH (Anteraper et al., 2021; Bak et al., 2018; Chaganti et al., 2017; Ipser et al., 2015) indicating a broader pattern of disruption in HIV. Morover, a study using a machine learning algorithm reported that salience, frontal parietal and parietal memory networks differentiate PWH with cognitive impairment from controls (Luckett et al., 2021). Overall, evidence demonstrates that reduced functional connectivity, as well as atrophy in both gray and white matter in cortical and subcortical regions are the most common indicators of brain injury in PWH.

Whether viral suppression with ART prevents the development of brain abnormalities remains unclear. Sanford, et al. (2018) compared PWoH individuals to PWH with chronic infection (average disease duration of 20 months) and primary infection (average disease duration of 3.7 months), who were followed longitudinally for an average of 5 months. Results revealed that PWH who initiated ART during primary infection had similar volumetric measures in brain gray matter compared to PWoH. Interestingly, small increases in cortical thickness measures were observed in participants with primary infection after 6 months of ART (Sanford, Ances, et al., 2018). However, longer duration of untreated infection resulted in significantly lower cortical and subcortical volumes in PWH compared to PWoH. By contrast, results from another study identified volume reduction in the basal ganglia over a two-year follow-up of individuals who initiated ART within 15 days of infection (Kallianpur et al., 2019). However, the previous study lacked a healthy comparison group. Thus, it is unclear whether the differences observed are greater than changes that may occur in PWoH. Cognition in PWH was similar to the normative data and remained stable in a later time point in

another study on primary infection (Longino et al., 2022). Overall, these studies suggest that some PWH have measurable abnormalities in brain structure despite early initiation of treatment, sustained use of ART, and viral suppression, though cognition may be spared. Additionally, other conditions that impact brain health, such as early life stressors (ELS), may differentially impact PWH prior to and during infection (Clark et al., 2012; Thames et al., 2018).

Correlates of ELS in HIV

ELS is prevalent worldwide. Before age 18, up to 70% of the global population reports at least one adverse life experience, either as a single or recurring event (Benjet et al., 2016; Houtepen et al., 2020), with ethnic minorities and other marginalized groups experiencing higher numbers of ELS events (O'Connor et al., 2019; Slopen et al., 2016). Examples of early life stressors include physical, sexual and emotional abuse, neglect, natural disasters, violence, parental separation, death of a family member, bullying and poverty (Brown et al., 2009; Pechtel & Pizzagalli, 2011). ELS represents a major risk factor for mental, behavioral, physical problems later in life, and early death (Felitti et al., 1998; Yu et al., 2022). ELS chronically increases cortisol levels, induces pro-inflammatory activity, and downregulates anti-inflammatory signaling (Nusslock & Miller, 2016; Slopen et al., 2013). These physiological changes are linked to structural and functional brain abnormalities that increase the risk for maladaptive cognitive processes, including risky decision-making, that increase disease morbidity and mortality. The process by which ELS induces negative long-term consequences in cognition and behavior is depicted in the Adverse Childhood Experiences Pyramid by the CDC (see Figure 1).

ELS which has been shown to produce epigenetic modifications of the human glucocorticoid gene (HGG; Parade et al., 2016; Tyrka et al., 2012; van der Knaap et al., 2014). These epigenetic changes to the HGG have been associated with alterations of brain structure and function (Gupta et al., 2016; Lieslehto et al., 2017; Malhi et al., 2019). Additionally, both chronic and acute stress can produce long-term alterations in the hypothalamic-pituitary-adrenal axis (Gunnar & Quevedo, 2007; Heim et al., 2009), resulting in pro-inflammatory reactions (Danese et al., 2007, 2009; Slopen et al., 2013; O'Connor et al., 2021). The resultant changes in the stress and immune response are believed to be the pathways by which ELS leads to reduced brain integrity (Kuhlman et al., 2017).

Studies reporting alterations in brain structure and function associated with ELS (Dannlowski et al., 2012; Hanson et al., 2012; Saleh et al., 2017) have variying results due to differences in brain regions of interest, age at the time of the adverse experience, and methodology used to ascertain ELS history (Calem et al., 2017; Lim et al., 2014; Herzog et al., 2020). Nonetheless, numerous studies have identified cortical and subcortical brain regions that appear to be susceptible to ELS (e.g., amygdala, insula, anterior cingulate, hippocampus, caudate, cerebellum, and the orbitofrontal, temporal, and parietal cortices; Andersen & Teicher, 2008; L. M. Baker et al., 2013; Carballedo et al., 2012; Chaney et al., 2014; Cohen et al., 2006; Dannlowski et al., 2012; Frodl et al., 2017; Gerritsen et al., 2015; Gorka et al., 2014; Kuhn et al., 2016; Kühn & Gallinat, 2013; Lim et al., 2018; Nardo et al., 2010; Tottenham & Sheridan, 2010; Ancelin et al., 2021; Clausen et al., 2019). Brain volumetric reductions have been related to alterations of the neuroendocrine stress response in individuals with ELS. For example, a

longitudinal study of children who experienced negative parenting (i.e., maternal hostility, neglect, and/or maternal negative affect during early childhood) showed higher cortisol reactivity to a stressor and lower hippocampal volumes compared to a control group (Blankenship et al., 2019).

PWH report a higher number of adverse childhood experiences compared to demographically similar PWoH (Pence et al., 2012). Several studies have examined interactions between ELS and HIV on brain structure and function (L. Baker, 2017; Clark et al., 2012, 2017, 2018; Spies et al., 2016; Thames et al., 2018), three of which reported that the combination of HIV and ELS is associated with smaller regional brain volumes (Clark et al., 2018; Spies et al., 2016; Thames et al., 2018). Thames et al. (2018) reported smaller volumes in the amygdala and hippocampus among PWH on ART with ELS experiences such as childhood poverty and/or racial discrimination when compared with PWoH and PWH without ELS. However, Clark et al. (2012) reported increased amygdala volume in PWH with high ELS (≥3 events). Larger amygdala volume correlated with lower nadir CD4+ T-cell count, indicating a relationship between HIV disease burden prior to ART and altered amygdala volumes (Clark et al., 2012). In an additional study of females only, lower grey matter volume was observed in the hippocampus, corpus callosum, caudate, putamen, and anterior cingulate (ACC) in women with HIV and ELS compared to both controls, and HIV-positive women without ELS (Spies et al., 2016).

Differences in viral load could be one of the factors associated with differences in brain volumes. Notably, viral load detectability and ART status differed between all three studies such that almost half of the PWH sample in Thames et al. (2018) had a detectable viral load, while in Clark et al. (2012), 16% of the PWH were ART-naïve and 26% had a

detectable viral load. In Spies et al. (2016) 52% of the participants (all of whom were female) were ART-naïve. A later study by Clark et al. (2018) in which 47% of the participants had detectable viral load revealed that PWH with high ELS compared to PWH with low ELS had lower total grey matter volume in cortical, subcortical, and cerebellar regions. ELS status explained 9% of the variance of grey matter volume reductions, and nadir CD4+ T-cell count accounted for an additional 7% of the variance (Clark et al., 2018). In contrast, another study showed no differences in volumetric measures of the hippocampus, corpus callosum, caudate, putamen, ACC, and amygdala in treated PWH with ELS, of whom 18% showed detectable viral load (Baker, 2017).

The inconsistent results from previous studies of HIV and ELS likely reflect methodological differences including heterogeneous study samples with regard to HIV treatment status, detectable viral load (Clark et al., 2012; Spies et al., 2016; Thames et al., 2018), co-morbid psychiatric symptoms (Clark et al., 2012; Thames et al., 2018), and/or co-morbid health conditions such as hepatitis C (HCV; Clark et al., 2012). Further, studies also differed in the way that ELS and brain volumes were measured (Clark et al., 2012; Spies et al., 2016; Thames et al., 2018). For example, in one study brain shape was the outcome measure, rather than brain volume (Thames et al., 2018; Clark et al., 2012; Spies et al., 2016). In the same study ELS was defined as poverty and perceived ethnic discrimination (Thames et al., 2018) whereas other studies focused more on child abuse and other forms of family trauma (Clark et al., 2012; Spies et al., 2016). To date, the effect of ELS on brain volumes in a virologically well-controlled PWH sample who do not have psychiatric or other co-morbid disease has not been addressed. Research is needed to determine the interactive effect of ELS and HIV pathogenesis on gray and

white matter brain structures without key confounding variables (Clark et al., 2012, 2018; Spies et al., 2016; Thames et al., 2018). Additionally, advances in clustering analyses can be used to differentiate subgroups of PWH with ELS with different brain morphology and cognitive outcomes.

Combined effects of HIV and ELS on cognition

Whether HIV and ELS have interactive effects on cognition remains inconclusive. For example, a study found interactive effects of ELS and HIV on learning and memory (Thames et al., 2018), and another study revealed that women with HIV and ELS had a greater decline in executive function over a one-year period than women with HIV but without ELS (Spies et al., 2017). However, other studies have not revealed interactions or associations between HIV and ELS on cognitive performance (Clark et al., 2012; Spies et al., 2016; Clark et al., 2022). Similar to the inconsistencies in brain volumes reported in prior studies, inconsistencies in cognitive outcomes among PWH with ELS vs. PWH without ELS are likely related to sample and methodological differences (Clark et al., 2012, 2018). No studies have explored the potential presence of distinct subgroups of PWH with ELS. Furthermore, research has focused primarily on traditional measures of cognitive functioning such as executive function, memory, and verbal fluency when examining HIV and ELS interactions, but not real-world measures affected by cognitive abilities, such as engagement in risky behaviors. Independent effects of HIV and ELS on risk-taking behaviors has been studied using monetary risk-taking tasks (De Bellis et al., 2013; Smith et al., 2018; Thames et al., 2012; *V*assileva et al., 2013). However, studies have not examined the combined effects of ELS and HIV on real world measures of risk-taking.

Previous findings suggest that individuals with both HIV and ELS are prone to engage in more risk-taking behaviors than individuals with HIV or ELS alone (Anderson et al., 2016; L. M. Baker et al., 2014). Risky behaviors are an important clinical and public health concern in HIV because increased risk-taking behavior is associated with poor ART adherence and higher probability of HIV transmission (Holstad et al., 2016; Kalichman, 2003; Kalichman et al., 2010; Ndziessi et al., 2012; Remien et al., 2007; Wilson et al., 2002). Furthermore, viremia secondary to poor ART adherence has been associated with neuronal damage (Gisslén et al., 2005) and cognitive impairment (B. W. Becker et al., 2011), which in turn, increases the risk of poor health outcomes. There has been surprisingly little research focused on the biopsychosocial determinants (e.g., ELS and brain signatures) of decision-making among PWH. This knowledge gap is important considering that most PWH became infected through risky behaviors such as intravenous drug use and/or unprotected sexual intercourse (amfAR, 2018).

Risky Decision-Making in HIV and ELS

Risk-taking behavior has been defined as "any consciously or non-consciously controlled behavior with a perceived uncertainty about its outcome, and/or about its possible benefits or costs for the physical, economic or psycho-social well-being of oneself or others" (Trimpop, 1994). Risk-taking behavior typically involves alterations in one or more of the following cognitive operations: cognitive processing shifts towards short term goals (S. M. Mueller et al., 2017), altered reward valuation (Anderson et al., 2016; Weller & Fisher, 2013), maladaptive use of cognitive strategies to regulate affect (Messman-Moore et al., 2010), and altered risk assessment (Johnson et al., 2016; Weller & Fisher, 2013). Risk-taking behaviors have long-term adverse consequences, such as the

development of substance use disorders and the transmission of infectious diseases, including HIV and HCV (Hakre et al., 2015; Jacka et al., 2019; Treloar Padovano et al., 2019).

In the context of HIV, the health/safety domain of risky behaviors, primarily focused on sexual behavior and substance use, has unique relevance (Blais & Weber, 2006). Risky sexual behavior is any sexual activity that increases the odds of unwanted pregnancies or sexually transmitted diseases, such as unprotected vaginal, oral, or anal intercourse. To date, most research on high-risk sexual behavior and risk of HIV has focused on unprotected sexual intercourse and increased number of lifetime partners (Buttmann et al., 2011). PWH report increased risky sexual behavior compared to uninfected persons (Baker et al., 2014), and PWH with ELS report higher risky sexual behavior than PWH without ELS (Bekele et al., 2018; Brezing et al., 2015; Pence et al., 2012). Whether the presence of HIV and ELS have an additive (sum of independent statistical effects) or synergistic effect (combined effect greater than the sum of the effects) remains unknown. However, some authors conclude that both HIV infection and early life adversity in conjunction with social determinants of health constitute a syndemic, characterized by two or more concurrent conditions that biologically interact synergistically leading to increased severity of the disease (Bekele et al., 2018; Dyer et al., 2012; Kidman et al., 2018). For example, in PWH, sex-risk behaviors are associated with lower treatment adherence and worse disease outcomes, which may reflect a common substrate related to poorer executive function (Kalichman, 2003; Kalichman et al., 2010; Mellins et al., 2011; Ndziessi et al., 2012; Cooley et al., 2020).

ELS and HIV both impact regions of the brain known to mediate risk-taking behavior, such as the ACC, amygdala, caudate, hippocampus, insula, and frontal and parietal lobes (Aydogan et al., 2021; Takeuchi et al., 2018; Feldstein Ewing et al., 2018; Grant et al., 2015; Seok & Sohn, 2018; H. Wang et al., 2015). Numerous studies demonstrate that individuals prone to risky decision-making show reduced volumes and altered functional activity in these brain regions (Feldstein Ewing et al., 2018; Goldenberg et al., 2013; Grant et al., 2015; Helfinstein et al., 2014; Seok & Sohn, 2018; H. Wang et al., 2015; Xue et al., 2018; Aydogan et al., 2021; Takeuchi et al., 2018). Individuals with damage to the insula, amygdala, parietal, and orbitofrontal regions performed worse on a behavioral task that measures risky decision-making known as the Iowa Gambling Task (IGT; Bechara et al., 1999, 2000; Ouerchefani et al., 2017). Poor performance on the IGT reflects an impaired ability to identify the relationship between actions and adverse consequences (Brand et al., 2007). A recent study evidenced that lower resting cerebral blood flow to the prefrontal cortex, insula, and posterior cingulate in PWH was associated with worse performance on the IGT; PWH with higher cerebral blood flow in these regions had a similar performance to PWoH (Smith et al., 2018). Risk-taking behavior on the Balloon Analogue Risk Task (BART; Lejuez et al., 2002) has been linked to lower volumes in the orbitofrontal cortex (OFC) and hippocampus (Iudicello et al., 2013; Strenziok et al., 2011; Huo et al., 2020). Risk-taking tasks and related brain changes often align with many cognitive domains. For example, attention and working memory, which support executive function, are often associated with risky behaviors (Pleskac, 2008; Schuster et al., 2012; Wilson et al., 2022). Additionally, executive function can contribute to poor performance in risk-taking tasks and be

associated with abnormal signatures of the brain reflecting functional decrements (Gu et al., 2018; Ouerchefani et al., 2017; Huo et al., 2020).

Ratings of health-related risky decision-making are associated with frontoparietal and fronto-subcortical regions that form a network involved in executive control and socio-emotional processing (Cox et al., 2010; Gluth et al., 2015; Helfinstein et al., 2014; Seok & Sohn, 2018). Relatedly, compared to controls, PWH and individuals with ELS demonstrate worse performance on both executive control and socio-emotional processing tasks (Baldonero et al., 2013; du Plessis et al., 2015; Mackey et al., 2017; S. C. Mueller et al., 2010). The corpus callosum, cingulum bundle, inferior fronto-occipital fasciculus (IFOF), and the superior longitudinal fasciculus (SLF) connect brain regions involved in executive control and socio-emotional processes; reduced integrity in these white matter tracts is associated with the presence of both HIV and ELS (Alm et al., 2015; Choi et al., 2012; M. J. Kim, Elliott, et al., 2019; Paul et al., 2017a; Samboju et al., 2018; Tendolkar Indira et al., 2018; Zorlu et al., 2013; Chang et al., 2020).

Diffusion Based Spectrum Imaging

As previously indicated, both HIV and ELS white matter injury are believed to be driven by neuroinflammation, however, neuroinflammatory markers of white matter integrity in PWH with history of ELS have remained unexamined. Diffusion tensor imaging (DTI) has been widely used to examine HIV-associated microstructural brain abnormalities (Chang et al., 2020; Cysique et al., 2017; Nakamoto et al., 2012; Paul et al., 2017b; Samboju et al., 2018; Wright et al., 2015; Strain et al., 2022). DTI measures the rate and direction of water diffusion along myelinated axonal fibers based on the principle that water diffuses in a directionally restricted manner in healthy neurons

whereas non-directional diffusion of water molecules indicates compromised myelin sheaths. However, DTI is unable to differentiate the multiple sources of signal change observed at the voxel level. Alternatively, diffusion basis spectrum imaging (DBSI) employs an algorithm to model voxel-wise white matter diffusivity using the DTI metrics axial diffusivity (diffusion parallel to axonal fibers) and radial diffusivity (diffusion perpendicular to axonal fibers), which are indicators of axonal integrity and myelin integrity (Song et al., 2002, 2003). DBSI is capable of distinguishing water diffusion properties such as axonal loss, cellularity (infiltrating cells as a neuroinflammation marker), and demyelination by isolating restricted water diffusion associated with neuroinflammation from the directional restricted diffusion (anisotropic) corresponding to axonal integrity (Y. Wang et al., 2015). DBSI has been validated as a proxy measure of neuroinflammation in post- mortem animal models (Chiang et al., 2014; X. Wang et al., 2014; Yang et al., 2021).

DBSI has been utilized to quantify neuroinflammation and white matter alterations among individuals with multiple sclerosis, obesity, as well as those with Alzheimer's disease, and HIV (Samara et al., 2020; Strain et al., 2017; Q. Wang et al., 2019; Y. Wang et al., 2011a, 2015; Vavasour et al., 2022). DBSI-derived cellularity has been related to microglial activation and astrogliosis in multiple sclerosis (Chiang et al., 2014; X. Wang et al., 2014; Y. Wang et al., 2015). A study on early stages of Alzheimer's disease showed that increased cellular diffusivity (reflecting cell size) was associated with cerebrospinal fluid t-tau level (a neurodegeneration marker) suggesting that increased cell body size of microglia/astrocyte is related to higher neurodegeneration (Q. Wang et al., 2019). Another study on multiple sclerosis associated higher cellularity

with higher levels of serum neurofilament light chain (proteins released by neurons in response to brain injury and neurodegeneration)(Yik et al., 2022). Moreover, increased cellularity, indicating neuroinflammation, throughout the brain was detected in virally suppressed PWH compared to PWoH (Strain et al., 2017). However, cellularity did not correlate with executive function, duration of infection or with HIV clinical measures such as nadir CD4+ T-cell count. Taken together, previous research suggests that DBSI is a neuroimaging technique sensitive to inflammatory changes in the CNS of PWH and other conditions related to neuroinflammation. Thus, DBSI metrics may provide additional information about mechanisms underlying brain atrophy in PWH with ELS.

Machine Learning

Brain abnormalities and cognitive performance of PWH vary greatly despite treatment. This variability may reflect diverse groups within PWH characterized by a combination of factors including pre-existing conditions, and co-occurring comorbidities such as ELS. Machine learning algorithms are efficient in revealing patterns that differentiate subgroups. These advanced algorithms perform a deeper level of clustering by discovering non-linear relationships of explanatory factors, interactions, etc., beyond known conceptual models (Basile & Ritchie, 2018; Mwangi et al., 2014). Unsupervised learning is a type of machine learning algorithm used to infer patterns within datasets without reference to known outcomes. The most common unsupervised learning method is cluster analysis which identifies intrinsic patterns within the data and variables that define clusters. The main goal of the technique is to group the observations into clusters where within group variation is minimized while across group variation is maximized. Unsupervised clustering methods have successfully identified clinical

phenotypes in HIV, depression, bipolar disorder, schizophrenia, dementia, and aphasia using demographic data, subjective reports, neuropsychological measures, and neuroimaging data (Cleret de Langavant et al., 2018; Feder et al., 2017; Paul et al., 2022; Sugihara et al., 2017; Wu et al., 2017). However, no studies have employed unsupervised clustering to determine whether a specific HIV/ ELS clusters exists and the underlying features that define the clusters.

One unsupervised clustering method is a Hierarchical Density-Based Spatial Clustering of Applications with Noise (HDBSCAN) algorithm which identifies a hierarchy of clusters of multidimensional variables to represent the data based on density-based approach (i.e., identifies clusters of the data that are denser than the surrounding space). HDBSCAN is a non-parametric method that computes a cluster hierarchy shaped by the multivariate modes of the underlying distribution and reveals intrinsic patterns that are not evident using traditional methods (Campello et al., 2015). This approach is unique among cluster-based approaches because it is robust to noise and outliers and identifies clusters of different shapes and sizes with different densities. HDBSCAN has been successfully applied to detect clinical outcomes of stroke on diverse groups of variables such as risk factors, clinical data, and neuroimaging data (Lin et al., 2019). Furthermore, HDBSCAN has been used to identify cognitive subtypes in PWH (Paul et al., 2022), suggesting that HDBSCAN is a suitable method to uncover data-driven combinations of variables that define an HIV and ELS subgroups.

Gaps in the Conceptual Framework of HIV and ELS

It remains unclear whether ELS potentiates brain abnormalities in PWH. Previous studies show differential results indicating a possible interaction between HIV and ELS

on brain morphometery, however the studies did not control for important confounding variables such as clinical depression, HCV, differences in ART treatment status, and degree of viral suppression, all of which have been demonstrated to affect brain integrity (Clark et al., 2012; 2018; Spies et al., 2016; Thames et al., 2018; Baker, 2017). Additionally, previous research has not focused on white matter tracts connecting gray matter regions involved in risky decision-making, such as the anterior corpus callosum, cingulum bundle, IFOF, and SLF (Alm et al., 2015; Choi et al., 2012; M. J. Kim, Elliott, et al., 2019; Paul et al., 2017b; Samboju et al., 2018; Tendolkar Indira et al., 2018; Zorlu et al., 2013).

Neuroimaging correlates of risky decision-making and sex-related risk-taking in PWH and ELS have not been studied. Given the high frequency of ELS in PWH (Pence et al., 2012), it is of crucial importance to determine whether ELS corresponds to self-reported history of risky sexual behavior in PWH without psychiatric symptomatology and other comorbidities, such as HCV, stroke, and progressive multifocal leukoencephalopathy. Further, whether ELS and executive function moderate the association between brain morphometry and sex-risk behavior is unclear. High rates of sex-risk behaviors in PWH might be due to the synergistic impact of ELS in brain volumes and executive function. Defining brain markers of PWH with ELS could identify at-risk phenotypes and underlying mechanisms to support the development and implementation of novel intervention strategies to reduce maladaptive behaviors and unfavorable long-term health outcomes.

Machine learning clustering methods are well suited to identify subgroups of ELS in HIV that otherwise might remain undetected using traditional statistical methods

(Miller et al., 2016). Data-driven approaches have been successfully implemented in HIV samples to detect patterns of cognitive and brain abnormalities in PWH (Petersen et al., 2021, 2022, Luckett et al., 2019, 2021; Ogishi & Yotsuyanagi, 2018; Paul et al., 2022; Paul et al., 2021; Paul, Cho, Belden, et al., 2020; Paul, Cho, Luckett, et al., 2020; Wade, Valcour, Busovaca, et al., 2015; Wade, Valcour, Wendelken-Riegelhaupt, et al., 2015; Zhang et al., 2016; Tu et al., 2019; Xu et al., 2021). Previous work has not investigated HIV and ELS using a multidimensional approach that could provide information needed to understand pathogenesis or guide optimal clinical management of HIV.

Summary

The majority of PWH in the United States are exposed to a diverse range of adverse childhood experiences (Pence et al., 2012; Reisner et al., 2011; Rodriguez-Penney et al., 2013). However, whether the combined effect of ELS and HIV potentiates brain atrophy in PWH is unclear. The combined effects of HIV and ELS need further examination as the effects of several factors are still unknown. These factors include neuroinflammation—which imaging markers such as DBSI cellularity can be used as a proxy—and risky decision-making. Whether self-reported sex-risk behaviors are associated with brain atrophy has not been examined. Furthermore, no existing studies have implemented a data-driven method to discover a combination of variables that define clusters of ELS and HIV. The present study addresses these gaps by examining gray matter integrity, DBSI cellularity, risky decision-making performance, and sex-risk behaviors in 164 PWH and 124 PWoH with high (≥ 3 events) or low (< 3 ELS events) ELS exposure from existing archival data. Additionally, in this study, the sample of PWH was restricted to individuals who had undetectable viral loads and no evidence of current

psychiatric or neurological illness. The overarching goal of the current study is to understand the relationship between ELS and HIV on neuroimaging markers and sex-risk behavior in PWH in the context of viral suppression.

Research Design Considerations

The first consideration was related to ELS assessment. Although retrospective measures may be influenced by normal forgetting, response bias or error in recall (Hardt & Rutter, 2004; Maughan & Rutter, 1997), prior studies using self-report scales such as the ELS Questionnaire (ELSQ) have successfully identified brain related phenotypes of ELS (L. M. Baker et al., 2013; Cohen et al., 2006). Further, the ELSQ has been used in previous studies to assess interactions of ELS and HIV, which allowed for comparisons across studies (Clark et al., 2012, 2017, 2018).

The second consideration was the definition of ELS. To account for single stressful events that might not have a significant impact in the developing brain, some studies have utilized a threshold of at least three or more self-reported events to define ELS (Clark et al., 2012, 2017; Paul et al., 2008). Although three or more ELS events may not be comparable between individuals, research has shown that experiencing three or more events is sufficient to detect brain atrophy in adulthood (Clark et al., 2012). As such, the current study designated individuals as low ELS if they reported zero to two ELS experiences before the age of 18, and high ELS if they endorsed at least three different adverse events. This approach allowed for direct comparison to prior work (Clark et al., 2012) and optimized the opportunity to detect significant group effects.

The third consideration was the selection of brain regions that were analyzed as dependent measures. The selection strategy is based on gray matter structures that are

susceptible to the effects of both ELS and HIV and have been associated with risk-taking behavior. Reduced volume in the ACC, insula, caudate, hippocampus, amygdala, OFC and parietal lobe have been reported in people with ELS (Carballedo et al., 2012; Chaney et al., 2014; Dannlowski et al., 2012; Edmiston et al., 2011; Hanson et al., 2010; Kelly et al., 2013; Lim et al., 2018; Saleh et al., 2017; Thomaes et al., 2010) and in PWH (Ances et al., 2012; J. T. Becker et al., 2012; Clark et al., 2012; Rubin et al., 2016; Sanford, Fellows, et al., 2018; Spies et al., 2016; Thames et al., 2018; Thompson et al., 2005). Furthermore, previous research examining interactions between ELS and HIV have not targeted the parietal lobe, a cortical region associated with risky decision-making (Grant et al., 2015; Helfinstein et al., 2014).

The final consideration was the selection of white matter tracts in which diffusion cellularity was examined. The selection strategy was based on white matter tracts that innervate brain regions susceptible to the effects of both ELS and HIV. The IFOF, the SLF, and the cingulum bundle are major white matter tracts that connect the frontal lobe with the parietal and temporal lobes. Findings suggest reduced integrity of these tracts is compromised in PWH (Samboju et al., 2018; Paul et al., 2017) and in populations with ELS (Kim et al., 2019; Tendolkar et al., 2018; Choi et al., 2011).

Aims and Hypotheses

<u>Specific aim 1</u>: Determine whether HIV infection and history of ELS interact to produce lower brain volume and higher cellularity in virally suppressed PWH with high ELS compared to PWoH or PWH with low ELS. H1a: PWH with high ELS (≥ 3 ELS events) will exhibit lower brain volumes in regions known to be vulnerable to the independent effects of HIV and ELS (e.g., ACC, insula, amygdala, caudate,

hippocampus, OFC and parietal lobe) compared to PWH with low ELS (< 3 ELS events) and PWoH independent of ELS history. **H1b:** PWH with high ELS will exhibit higher cellularity in tracts that connect fronto-parietal and fronto-subcortical brain regions such as the anterior corpus callosum, the cingulum bundle, the fronto-occipital fasciculus, and the SLF compared to PWH with low ELS and PWoH independent of ELS history.

Specific aim 2: Determine whether ELS interacts with HIV on risky decision-making and sex-risk behaviors in virally suppressed PWH. H2a: PWH with high ELS will report more frequent engagement in sex-risk behaviors over the past six months compared to PWH with low ELS and PWoH. **H2b:** PWH with high ELS will have increased risky decision-making on the BART and IGT compared to the other study participants. **H2c:** Lower brain volumes in PWH and ELS will be associated with increased self-report of sex-risk behavior, and worse performance on the BART and IGT IGT after covariate adjustment. **H2d:** Executive function will moderate the relationship between brain volumes and sex-risk behavior (Figure 2).

Exploratory aims

Exploratory aim 1: Determine whether clinical features of HIV and ELS status detect clinically meaningful subgroups in PWH using a data driven clustering analysis.

Approach

The current study utilized high-resolution neuroimaging (i.e., brain volumes and DBSI), self-report measures of ELS, cognitive measures (quality of education and executive function), depressive symptoms, and subjective and objective measures of past and current drug use to examine the impact of ELS on neuroimaging markers and risky

behavior (IGT, BART, and sex-risk behavior) among PWH. This study leveraged archival data acquired through studies funded by the National Institutes of Health (R01-NR012657; R01-NR012907; R01-NR014449; PI: Dr. Beau Ances).

Participants

Participants were recruited from local organizations, community medical providers, the Washington University School of Medicine (WUSM) AIDS Clinical Trial Group, and the WUSM Infectious Disease Clinic in Saint Louis. At the time of enrollment, PWoH were tested with a rapid oral HIV test to verify lack of HIV viremia. For PWH, HIV serostatus was tested by enzyme-linked immunosorbent assay and confirmation was obtained from Western blot test. To determine CD4+ T-cell counts and plasma HIV viral load, a blood sample was collected from all PWH within 30 days of neuroimaging and other study-related assessments. Nadir CD4+ T-cell count was ascertained from self-report or medical records, when available. PWH on ART with suppressed viral load ≤ 50 copies/mL were included in the study. The WUSM and the University of Missouri-St. Louis Institutional Review Boards approved the study protocol pursuant to the parent studies. All participants provided informed consent and received financial remuneration for participating in the study.

Inclusion and Exclusion criteria

Participants were native English speakers, with 8 or more years of education. Exclusion criteria for all participants included history of uncorrected abnormal vision, active major psychiatric illness (e.g., bipolar disorder, post-traumatic stress disorder, Major Depressive Disorder, etc.), developmental disability including learning disability, neurological illness (e.g., progressive multifocal leukoencephalopathy, stroke), HCV co-

infection, traumatic head injury with loss of consciousness >30 min, and current opportunistic infection involving the CNS. Participants were excluded if their urine toxicology screen was positive for any illegal substances except tetrahydrocannabinol (THC), but most participants tested negative. History of substance use was not exclusionary.

Study Procedures

All participants provided informed consent. Recent substance use was tested by performing a urine toxicology screen (cocaine, amphetamines, meth, opiates, methadone, THC, phencyclidine, barbiturates, tricyclic antidepressants and benzodiazepine). Participants were not excluded if tested positive for THC or benzodiazepine. Magnetic resonance imaging (MRI) neuroimaging was completed within one week of all other study procedures except for HIV lab indices which were within 30 days of all study protocols. Participants underwent neuropsychological assessment within one week of the neuroimaging scan. The neuropsychological tests included measures that are sensitive to the deleterious effects of HIV, ELS and risky behaviors such as learning, memory, psychomotor processing, verbal fluency, and executive function (Clark et al., 2012; Robertson et al., 2007; Thames et al., 2018).

Measures

Sex Risk Behavior Assessment

The Risk Assessment Battery (RAB; Metzger et al., 2001) is a 40-question self-report measure developed to assess risk-taking behaviors, such as unprotected sex and number of sexual partners, that are associated with HIV transmission risk. Both PWH and PWoH completed the RAB scale. The measure includes two subscales: total sex-risk

score and total drug risk score. In the present study, only the sex-risk subscale was included for analysis. Lifetime substance use was measured using the Kreek-McHugh-Schluger-Kellogg scale (KMSK) for inclusion as a covariate. Reports of condom use in the past six months, and number of sexual partners in the past six months and lifetime were used as a measure of risky sexual behaviors based on previous research on risky behavior (Buttmann et al., 2011; Jackson et al., 2019; Metzger et al., 2001). Condom use was entered as four categories: Always or no sexual intercourse, most of the time, sometimes and never. Participants that only reported one lifetime partner and no condom use were assigned to the "Always" category for condom use in the past six months with the assumption they were in a committed relationship as relationship status was not assessed. Based on the RAB and previous research (L. M. Baker et al., 2014; Metzger et al., 2001), four categories were created to ascertain the number of sexual partners in the past six months and lifetime. Sex partners in the past six months were categorized into 0, 1, 2-3, 4 or more partners according to the RAB, and lifetime sexual partners were categorized into 0-1, 2-4, 5-9, 10 or more according to previous research (Buttman et al., 2011; Jackson et al., 2019).

Early Life Stress Assessment

ELS was assessed using the 19-item ELSQ (Cohen et al., 2006), which evaluates experiences of family conflict, neglect, physical abuse, sexual abuse, bullying, and other potentially traumatic experiences before 18 years of age. Low ELS was defined as fewer than three adverse childhood experiences, and high ELS was defined as three or more ELS experiences, consistent with previous neuroimaging research on ELS (Cohen et al., 2006; Gerritsen et al., 2015).

Depression Assessment

The Beck Depression Inventory II (BDI-II; Beck et al., 1996) is a 21-item questionnaire that evaluates the presence and severity of depressive symptoms. Scores are defined as follow: 0–13 minimal depression, 14–19 mild depression, 20–28 moderate depression, and 29–63 severe depression (Beck et al., 1996). The BDI-II was used to exclude participants with severe symptoms of depression (total score ≥ 29), due to the negative effects of severe symptoms of depression on decision-making, brain morphometry and neuroinflammation (Kuzior et al., 2020; Murphy et al., 2001; Wise et al., 2017). The psychometric properties of the BDI-II have been validated (Hobkirk et al., 2015) and applied in numerous studies of HIV (Antoni et al., 2006; Hoare et al., 2011; Ironson et al., 2015; Paul et al., 2017b, 2018; Thames et al., 2012, 2018).

Substance Use Assessment

Substance use history was assessed with the KMSK scale (Kellogg et al., 2003). The KMSK has been employed in many HIV studies (Bryant et al., 2015; Clark et al., 2012, 2018; Devlin et al., 2012; Fogel et al., 2017; Heaps-Woodruff et al., 2016; Martin et al., 2016). The original KMSK scale captures heaviest use during lifetime of four substances (alcohol, cocaine, heroin, and tobacco) through self-report of frequency, amount, and duration for each substance. A revised version of the KMSK (Butelman et al., 2018; Tang et al., 2011) includes a measure of cannabinoid use but was not implemented at the time of this study, therefore, many participants in the present study lack the marijuana KMSK data. As such, current THC use was assayed via urine drug screen and coded into a dichotomous variable based on positive or negative urine toxicology.

Quality of Education

The Wide Range Achievement Test-3 (WRAT-3; Wilkinson, 1993) measures reading, arithmetic, and spelling core skills from ages 5 to75 years. This study included the reading sub-test only which has been demonstrated in previous studies to be a valid proxy measure of education (Sayegh et al., 2014). In the reading test participants are required to read out loud 42 individual words that are presented with increasing difficulty and 15 letters. If participants are unable to read the first three words, they are asked to identify the letters on the alphabet. The number of total correct words is the outcome measure.

Executive Function

Trial 3 from the Color Word Interference Task (CWIT) of the Delis-Kaplan Executive Function System (Delis et al., 2001) was used as a measure of executive function. CWIT trial 3 consists of four rows of color names (e.g., the word “blue”) printed in different ink color from the word meaning (e.g., the word “green” printed in red ink). Participants are required to say out loud as fast as possible the color in which each word is printed instead of reading the word. Completion time is the primary outcome measure.

Risk-Taking Tasks

Iowa Gambling Task (IGT)

Participants were administered a computer-based version of the IGT. The IGT displays four decks of cards. Participants were instructed to select one card from the four decks on each trial with the goal of maximizing profit with every choice resulting in either financial reward or financial penalty. The amount of money won or lost on each

trial was displayed on the screen. The task requires participants to select cards from two "good" decks with smaller rewards and smaller penalties and to avoid the other two "disadvantageous" decks with larger rewards and larger penalties (Bechara et al., 1994). A total of 100 trials were administered subdivided into five blocks of 20 trials. The primary outcome measure is calculated by subtracting the number of bad choices from the number of good choices across all trials (Wardle et al., 2010). The IGT has been used in HIV and ELS studies independently to determine whether PWH performs worse in risk-taking tasks associated with poor cognitive function (Iudicello et al., 2013; Paydary et al., 2016; Smith et al., 2018; Thames et al., 2012; Welsh et al., 2017).

Balloon Analogue Risk Task (BART)

The BART presents a balloon on the screen with the chance to build a simulated bank of money by increasing the size of the balloon and cashing out before the balloon bursts. The simulated bank of money zeros out if the balloon bursts. The average number of successful responses (pumps) prior to the explosion of balloons is the primary outcome measure, with more pumps indicating greater risk-taking behavior (Bornovalova et al., 2008; Lejuez et al., 2002). The BART has been employed to measure risk-taking in PWH and individuals with ELS (Augsburger & Elbert, 2017; S. T. Kim et al., 2018; Paydary et al., 2016). Some studies have paid the participants in cash or certificates for the amount of money earned in the BART in order to reflect more accurately the positive and negative consequences of the decisions made during the task (Lejuez et al., 2002; Augsburger & Elbert, 2017). In the present study participants did not receive a monetary reward for this specific task.

Summary of Cognitive Tests

Domain	*Measurement Tool*	*Outcome Measure*
Executive Function	Color-Word Interference Task (CWIT)	Trial 3- time to completion
Risk-Taking Tasks	Iowa Gambling Task (IGT)	Total number of good choices minus bad choices
	Balloon Analogue Risk Task (BART)	Total number of pumps with no explosion

Neuroimaging

Neuroimaging Acquisition

This study leveraged archival neuroimaging data. Imaging acquisition was performed at WUSM using a 3T Siemens Tim Trio whole-body MR scanner (Siemens AG, Erlangen Germany) with a 12-channel transmit/receive head coil. Structural whole-brain MRI scans were collected using a T1-weighted three-dimensional magnetization-rapid acquisition gradient echo (MPRAGE) sequence (time of repetition/inversion time/echo time = 2400/1000/3.16 ms, flip angle=8°, and voxel size=1 x 1 x 1 mm^3) for volumetric analysis. Two acquisitions of diffusion-weighted images (DWIs) were obtained (2 x 2 x 2 mm^3 voxels, TR= 9900 ms, TE = 102 ms, flip angle =90°, 23 directions with multiple b values ranging between 0 and 1400 s/mm^2) for DBSI measures.

Volumetric Analysis

Volumetric measures were acquired using the FreeSurfer software suite (v5.3; Martinos Center, Harvard University, Boston, MA; http://surfer.nmr.mgh.harvard.edu). The FreeSurfer program strips the skull from the MPRAGE scans and fits the skull into a template space to then perform a brain segmentation of white matter, gray matter, and ventricles. A surface deformation program was used for brain parcellation (Dale et al., 1999; Desikan et al., 2006; Fischl et al., 1999). Each image was registered to the atlas

MNI305 (Fischl et al., 2004). Regions of interests included the caudate, amygdala, hippocampus, insula, OFC, and parietal lobe based on results from prior studies (Spies et al., 2016; Clark et al., 2012; Thames et al., 2018). All brain volumes were corrected for head size before analysis using a linear regression between each brain volume and total intracranial volume to predict head size adjusted bilateral volumes.

Image Pre-Processing for Diffusion Based Spectrum Imaging (DBSI)

Study personnel reviewed scans for excessive movement prior to processing. Images that did not exceed movement thresholds (>3mm) were corrected for eddy current distortions followed by skull stripping using FSL 5.0.9.34.

DBSI Processing

DBSI metrics were estimated on the DWIs employing in-house software scripted in MATLAB (MATLAB and Statistics Toolbox Release, 2012) as explained in previous research (Samara et al., 2020; Strain et al., 2017; Y. Wang et al., 2011b). The total diffusion signal (S_k) derived from DBSI contains both anisotropic (A_k) and isotropic components. The DBSI equation expresses the weighted sum of these components, in which S_k and b_k are the signal and b-value of the k^{th} diffusion gradient, N_{Aniso} is the number of anisotropic tensors, Φ_{ik} is the angle between the principal direction of the i^{th} anisotropic tensor and the k^{th} diffusion gradient, $\lambda_{\|i}$ and $\lambda_{\perp i}$ are the axial diffusivity and radial diffusivity of the i^{th} anisotropic tensor, f_i is the signal intensity fraction for the ith anisotropic tensor, and a and b are the low and upper diffusivity limits for the isotropic the diffusion spectrum $f(D)$. Isotropic diffusion includes both restricted diffusion (cellularity), and unrestricted isotropic diffusion (extracellular space). Cellularity is defined by an upper limit (b) of 0.3 $\mu m^2/ms$ while extracellular diffusion is calculated

when the limit is greater than 0.3 μm^2/ms. (Y. Wang et al., 2011b, 2015). Cellularity was the primary DBSI outcome measure used in analyses.

Statistical Analyses

All statistical analyses were conducted using Statistical Package for the Social Sciences version 27 (SPSS 27, IBM Corp, 2020). Data were screened for outliers and missing values prior to statistical analyses. Outliers were defined using Tukey's method by excluding values +/-1.5 times the interquartile range above or below the adjusted quartile ranges (Jones, 2019; Tukey, 1977). The shape of the distribution of each variable was visually inspected using Q-Q plots and boxplots. Skewness and kurtosis were examined to assess the distribution of variables.

The distribution of lifetime cocaine and opiate use scores were skewed such that the vast majority of participants had zero use. As such, the scores were best managed by dichotomizing into used/not used as Q-Q plots and boxplots indicated that the abnormal distributions were independent of outliers. The Kruskal-Wallis H test was performed to compare differences between four groups for variables that were non-normally distributed such as age, self-reported lifetime alcohol and tobacco use. Demographic variables such as years of education and sex were examined across the four groups with one-way univariate analyses of variance and Chi-square. Differences in clinical variables including nadir CD4+ T-cell count, current CD4+ T-cell count and duration of infection were tested between both PWH with low ELS and PWH with high ELS groups using t-tests. The Kruskal-Wallis H test was used to compare the difference in viral load, and the Spearman's Rho correlation was employed to test the association between two non-parametric variables. Multicollinearity among variables was evaluated, with the tolerance

threshold set at 2.5 (Allison, 2012) to determine if non-parametric measures for analysis were needed. However, no variables had tolerance values > 2.5 and Cook's distance < 1.

Specific Aim 1

H1a: *PWH with high ELS (≥ 3 ELS events) will exhibit lower brain volumes in regions known to be vulnerable to the independent effects of HIV and ELS (e.g., ACC, insula, amygdala, caudate, hippocampus, OFC and parietal lobe) compared to PWH with low ELS (< 3 ELS events) and PWoH independent of ELS history.* Hierarchical least squares multiple regression analyses were performed for the dependent variables (brain volumes), with ELS exposure, HIV status, and propensity score serving as the independent variables. Propensity scores were entered into the first step of the regression model. HIV-status and ELS were included as independent factors in step 2. HIV status and ELSQ were dummy coded, and an interaction term was calculated (e.g., HIVxELS), which served as the interaction term. In the final step, the interaction term was entered. Brain volume regions served as the dependent variable. Statistical significance was initially determined using an alpha level of .05. False Discovery Rate (FDR; Benjamini & Hochberg, 1995) was performed for all multiple comparisons to correct for type 1 error.

H1b: *PWH with high ELS will exhibit higher cellularity in tracts that connect fronto-parietal and fronto-subcortical brain regions such as the anterior corpus callosum, the cingulum bundle, the IFOF, and the SLF compared to PWH with low ELS and PWoH independent of ELS history*. Interactive effects of ELS and HIV were examined with hierarchical least squares multiple regressions. HIV-status and ELS were included as independent factors in step 2. HIV status and ELSQ were dummy coded, and an interaction term was calculated, which served as the interaction term. In the final step,

the interaction term was entered. White matter tract cellularity served as the dependent variable.

Specific Aim 2

H2a*:* *PWH with high ELS will report more frequent engagement in sex-risk behaviors over the past six months compared to PWH with low ELS and PWoH.* Multinomial logistic or binary logistic regression analyses were performed for the dependent variables (RAB Sex Risk subscale), with propensity score, ELS exposure, HIV status and an interaction term serving as the independent variables. Post-hoc contrast analyses were employed in the regression models that displayed statistical significance to determine specific group effects on the RAB sex-risk score.

H2b: *PWH with high ELS will show more risky decision-making on the BART and IGT compared to the other study participants.* Interactive effects of ELS and HIV on sex-risk were examined with two hierarchical multiple regressions including covariates. Covariate and statistical assumptions were examined as described above. HIV status, ELS, and propensity score were included as independent factors in step 1 and 2. HIV and ELS status were dummy coded and an interaction term was calculated (e.g., HIVxELS). In the second and final step, the interaction term was entered. IGT and BART scores served as the dependent variable in independent models.

H2c: *Lower brain volumes in PWH and ELS will be associated with increased self-report of sex-risk behavior, and worse performance on the BART and IGT after covariate adjustment.* Partial correlations, adjusting for covariates (propensity score), were computed to determine the relationship between the risky decision-making (IGT, and BART) and volumetric measures in the overall sample and separated subsamples by

HIV status. One-way one-way analysis of covariance (ANCOVA) and a T-test were performed to test differences on volumetric by RAB sex-risk score category.

H2d: *Executive function will moderate the relationship between brain volumes and sex-risk behavior.* The Color-Word Interference Task (CWIT) Trial 3 was included in the moderation analysis as measure of executive function due to the association to sex-risk behavior (Barkley-Levenson et al., 2018). Domain-specific scores were not calculated as normative data were necessary. Although much effort has been put into creating pertinent norms, norms might not be adequate for all members of an ethnic group. For example, the Mayo's Older African Americans Normative Studies is based on older adults from Florida that were educated in southern segregated schools (Lucas et al., 2005). Additionally, there might be a generational effect in cognitive performance (Trahan et al., 2014), which would suggest the need for updated norms. Thus, the WRAT-3 was included to account for education quality. A subset of participants completed risk-decision tasks (IGT & BART). Multiple regression models were conducted to examine the relationship between brain volumes and sex-risk behavior (main effects) and whether these relationships are moderated by executive function (see Figure 2). Raw score from the CWIT Trial 3 was used as measure of executive function.

Covariate adjustment using propensity scores

In order to adjust for these potential confounders, a propensity score including covariates was calculated to reduce the number of covariates in the regression models examining the interactive effects of ELS and HIV on brain volumes. A propensity score can be calculated performing a logistic or multinomial regression where grouping status is predicted from covariates. Thus, a propensity score indicates the likelihood of a

participant being in a specific group based on covariate information (Austin, 2011; Rosenbaum & Rubin, 1984). Covariates that differ among groups but are not associated with the outcome may increase variance and bias if included in the propensity score (Brookhart et al., 2006). Therefore, variables that differ among groups but are not associated with the outcome are not beneficial to be included as covariates. Thus, variables included in the propensity score were any substance use, demographic, or clinical variables that had a statistically significant association with the outcome variable and significantly differed among groups. The use of a propensity score covariate index has shown to be advantageous in adjusting for confounders in small (sample < 50) and medium datasets (sample = 50-300) because the approach has minimal effect on statistical power (Austin, 2011; Elze et al., 2017).

Exploratory Aim 1: Cluster Analysis Methods

Duration of infection, nadir CD4+ T-cell count, recent CD4+ T-cell count and ELS high and low were features selected for the cluster analysis focusing on HIV related clinical variables and ELS status. As the selected cluster analysis algorithms can not analyze cases with missing values, multiple imputation was performed if data was missing less than 3% of scores to avoid deleting cases with missing values and further reducing the number of cases. Features were scaled by converting variables to Z-scores or dummy coding them before feeding into the algorithm for dimension reduction. Machine learning analyses were performed using python programing language module Scikit-learn for supervised and unsupervised algorithms (“Scikit-learn,” 2020; Pedregosa et al., 2011). As an initial step before HDBSCAN clustering, the Uniform Manifold Approximation and Projection (UMAP) machine learning dimensional reduction technique was applied.

UMAP reduced the data dimensions and projected it onto a 2D space creating embedding. UMAP is designed to predominantly preserve local structure of high dimensional data by grouping neighboring data points together using exponential probability distribution in high dimensions (McInnes et al., 2020) that provides an informative visualization of heterogeneity in the data and boosts the performance of density-based clustering (Allaoui et al., 2020). UMAP has been previously implemented in scientific studies for dimension reduction of high dimensional data (Ali et al., 2019; Becht et al., 2019; Dorrity et al., 2020; Paul et al., 2022).

Power Analysis

Statistical computation software G*Power (Faul et al., 2009) was used to calculate the required *N* from inputted parameters for all primary regression and moderation analyses. As the proposed study represents a novel extension of the extant literature, the power analyses were modeled using pooled effect sizes reported from prior studies that examined similar ELS and HIV interactions but not overlapping indices of neuroimaging variables. For Aim 1a, the power analysis was based on results from Spies et al. (2016), which identified medium-large effect sizes (Cohen's *d* 0.62 to 0.74). As a conservative approach, a small-medium effect size was modeled ($d = 0.30$) for a regression analysis with one covariate, and a *p*-value corrected for multiple comparisons using FDR approach. The power calculation indicated that the 79 PWH/high ELS, 43 PWH/low ELS, 57 PWoH/low ELS, and 55 PWoH/high ELS provided at least 85% power to detect differences in brain volumes. Aim 1b was based on results from Strain et al. (2017), which identified a large effect size ($d = 1.2$). Following a conservative approach, a small-medium effect size was modeled ($d = 0.30$) with inclusion of four

predictors (HIV-status, ELSQ, a covariate, and the interaction term HIVxELSQ). Results revealed that the available sample size of 89 PWH and 59 PWoH provided at least 85% power to detect differences in white matter cellularity.

Power analyses for Aim 2a were conducted using results from a prior study of sex risk behaviors among PWH (Baker et al., 2014), which reported an effect size of Cohen's d= 0.855. Assuming a small-medium effect size of d = 0.30, inclusion of one covariate in a regression analysis, and a p-value corrected using FDR, 79 PWH/high ELS, 43 PWH/low ELS, 57 PWoH/low ELS, and 55 PWoH/high ELS provided at least 85% power to detect higher sex-risk behaviors among PWH/high ELS compared to PWH/low ELS and PWoH. Aim 2b was based on results from Paydary et al. (2017) and Thames et al. (2012), which identified medium-large effect sizes (d = 0.61 to 0.70). A small-medium effect size was modeled (d = 0.30) with inclusion of four predictors (HIV-status, ELSQ, one covariate, and the interaction term HIVxELSQ). Results revealed that a sample size of 75 PWH and 48 PWoH provided at least 80% power to detect differences in executive tasks. Power analyses were conducted for Aim 2c using results from prior studies of the BART and IGT with healthy participants (Gansler et al., 2012; Nasiriavanaki et al., 2015). Results revealed that with a small effect size (d = 0.30), a sample of 235 individuals provided 85% power to detect associations on sex-risk behavior and a sample of 123 individuals provided 80% power to detect associations on the risky decision-making tasks with one covariate and p-value adjusted for multiple comparisons. Effect sizes (d= 0.62- 0.85) from studies examining the relationships between variables included in the moderation model (Corrêa et al., 2016; Reynolds et al., 2019) were used as reference for Aim 2d. Using a conservative effect size of d = 0.30, and two groups, a

total sample of 235 individuals provided at least 80% power to identify significant associations between neuroimaging variables and sex-risk score in the total sample moderated by executive function based on multiple regression analysis with one covariate and *p* value adjusted for multiple comparisons. Collectively these numbers indicated that the available sample provided sufficient power to confirm the hypotheses for each specific aim.

Results

Specific aim 1

Hypothesis H1a: Interactive effects of ELS and HIV on brain volumes

Preliminary Analyses

The total sample included 145 males (62%) and 90 females (38%) constituting an overall sample of 235 participants with a median age of 50 (*IQR* = 34.0; range = 18-73), of which 63 individuals (27%) were 18-25 years old, 41 individuals (17%) were 26-45 years old, 52 individuals were 46-55 (22%) years old, 62 individuals (27%) were 56-65 years old and 17 individuals (7%) were over 65. The average years of education was 13.64 (SD = 2.4; range = 8-20). Most of the participants were African American (55%), followed by Caucasian (43%), multi-racial (1%), American Indian (0.5%) and Asian (0.5%). ELS and HIV groups were similar in race distribution ($\chi^2(12, n = 235) = 9.99$, $p = 0.617$, Cramer's $V = 0.119$), educational attainment (*Welch's* $F(3, 117.42) = 0.29$, $p = 0.830$), quality of education as measured by the WRAT-3 ($F(3, 229) = 1.08$, $p = 0.356$), self-reported use of alcohol ($H(3) = 3.52$, $p = 0.318$), tobacco ($H(3) = 5.56$, $p = 0.135$), opiates ($\chi^2(3, n = 232) = 0.66$, $p = 0.883$) and THC urine sample ($\chi^2(3, n = 232) = 0.66$, $p = 0.883$). However, PWH groups were significantly older ($H(3) = 43.58$, $p < 0.001$), had

significantly more males than females ($\chi^2(3, n = 235) = 20.28$, $p < 0.001$, Cramer's $V = 0.29$) and self-reported higher levels of lifetime cocaine use ($\chi^2(3, n = 235) = 20.18$, $p < 0.001$) than PWoH groups. Additionally, more PWH reported more history of coinfections such as hepatitis B ($\chi^2(3, n = 233) = 26.71$, $p < 0.001$, Cramer's $V = 0.34$) and tuberculosis ($\chi^2(3, n = 233) = 10.52$, $p = 0.015$, Cramer's $V = 0.21$) compared to PWoH. More PWH tested positive for THC ($\chi^2(3, n = 235) = 11.50$, $p = 0.009$, Cramer's $V = 0.22$) than PWoH/low ELS. PWH/high ELS reported more history of hepatitis A ($\chi^2(3, n = 233) = 10.61$, $p = 0.014$, Cramer's $V = 0.21$) than PWoH. A higher percentage of PWH/high ELS had a positive urine sample for benzodiazepines ($\chi^2(3, n = 235) = 10.57$, $p = 0.014$, Cramer's $V = 0.21$) compared to PWoH. BDI-II score was higher in PWH/ high ELS than in PWoH/ low ELS $F(3, 231) = 4.21$, $p = 0.006$).

PWH reported more sexual abuse ($\chi^2(1, n = 235) = 5.49$, $p = 0.019$, Cramer's $V = 0.15$), emotional abuse ($\chi^2(1, n = 235) = 7.60$, $p = 0.006$, Cramer's $V = 0.18$) and death of a sibling ($\chi^2(1, n = 235) = 7.40$, $p = 0.007$, Cramer's $V = 0.18$) compared to the other groups. Mann-Whitney and T-tests indicated no difference among ELS subgroups in HIV-related clinical variables including duration of infection ($t(120) = -0.96$, $p = 0.337$), recent CD4+ T-cell count ($t(120) = 0.43$, $p = 0.324$), nadir CD4+ T-cell count ($t(107) = 0.91$, $p = 0.362$), viral load *(U(n* = 43, *n*= 79) =1839.50, $z = 1.59$, $p = 0.112$) (see Table 1).

The correlation analyses revealed a significant negative association between all volumetric variables and age ($p < 0.001$). Self-reported cocaine use and hepatitis B were negatively associated with the OFC, parietal lobe and caudate volumes ($p < 0.05$). Individuals with a positive urine test for benzodiazepine had lower parietal lobe volumes

($p < 0.05$). Women had significantly larger parietal lobes than men (mean difference = -3,833.25 cm^3, $p < 0.001$).

Results

After calculating a propensity score to control for age, cocaine use and hepatitis B history, results of the hierarchical multiple regression revealed a significant interaction between HIV and ELS status (Adjusted $R^2 = 0.17$, $p = 0.004$), with lower volumes in the OFC of PWH with high ELS compared to the rest of the groups and higher volumes in the PWoH with high ELS. This association remained significant after FDR correction. No statistically significant interactions between HIV and ELS status were observed in the remaining brain regions (see Table 2).

Significant HIV main effects were observed on the OFC ($\beta = -0.386$, $p \leq 0.001$), the parietal lobe ($\beta = -0.37$, $p \leq 0.001$), caudate ($\beta = -0.36$, $p \leq 0.001$) and the amygdala ($\beta = -0.14$, $p = 0.048$) such that PWH had lower brain volumes compared to the PWoH group. No statistically significant effects were found in the remaining brain volumes. No significant ELS main effects were observed on brain volumes.

Hypothesis H1b: Interactive effects of ELS and HIV on DBSI

Preliminary Analyses

In the subsample with the DBSI measure of cellularity (n =148), groups of PWH were significantly older *(H(*3) = 47.92, $p < 0.001$), included more males ($\chi^2(3, n = 148) = 18.20$, $p < 0.001$, Cramer's $V = 0.35$), self-reported more cocaine use ($\chi^2(3, n = 148) = 17.30$, $p < 0.001$, Cramer's $V = 0.35$) and history of hepatitis B ($\chi^2(3, n = 148) = 13.33$, $p = 0.004$, Cramer's $V = 0.30$). PWH/high ELS reported more symptoms of depression ($F(3, 144) = 4.10$, $p = 0.008$) than PWoH/low ELS (see Table 3). However, there were no

significant associations between sex, age, cocaine use or hepatitis B on measures of cellularity, therefore, HIV and ELS status were the only predictors in the model. No propensity score covariate was included in the model.

Results

Results of the hierarchical multiple regression revealed that the interaction of HIV and ELS status was statistically significantly associated with DBSI measures in the IFOF (Adjusted $R^2 = 0.04$, $p = 0.005$) and the cingulum (Adjusted $R^2 = 0.01$, $p = 0.044$). Specifically, higher cellularity in the inferior frontal-occipital fasciculus and the cingulum was observed in the PWoH with high ELS compared to PWoH with low ELS and PWH with high ELS, however the association of the cingulum did not remain significant after FDR corrections (see Table 4). No other interactions of HIV and ELS status were observed on brain cellularity. No statistically significant main effects were observed for ELS or HIV on brain cellularity.

Specific aim 2

Hypothesis H2a: Interactive effects of ELS and HIV on sex risk behavior

Preliminary Analyses

For the category condom use in the past six months, most participants (86%) were categorized into the lowest risk category (always use condom, no sexual intercourse or just having one partner), 5.5% of participants reported using condoms most of the time, 5.1% reported sometimes using condoms, and 3.4% reported never using condoms. The distributions of the sex-risk groups violated assumptions of multinomial regression. Therefore, groups of condom use in the past six months were collapsed into two categories. The lowest risk category remained the same (86% of participants) and the rest

three categories were merged to conform the second category (14% of participants). The use of covariates was not indicated. The trend differed for lifetime history of condom use, in which 21% of participants reported always using condoms or no sexual intercourse, 38% reported using condoms most of the time, 35% condom use sometimes, and 6% reported never using condoms. Individuals who reported inconsistent use condoms during lifetime were older *(H(*3) = 15.97, $p = 0.001$), and as such age was included as covariate.

The second measure of sex-risk behavior evaluated the number of partners in the past six months and total lifetime partners. Participants reported having 0 sexual partners (29%), 1 partner (49%), 2 or 3 partners (16%), and 4 or more partners (6 %) during the past six months. Individuals who reported having more than 1 partner in the past six months were younger *(H(*3) = 48.36, $p < 0.001$), therefore, age was included as covariate. Participants reported having 0-1 sexual partners (8%), 2-4 partners (26%), 5-9 partners (20%), or 10+ partners (46%) total lifetime partners. Groups were collapsed into three categories on total lifetime sex partners because group variance assumptions for multinomial regression were violated. Participants reporting having less than 4 partners were collapsed into one category (34% of participants) and the rest two categories remained the same. Individuals who reported having more sex partners during lifetime were older *(H(*2) = 8.61, $p = 0.013$). Thus, age was included as a covariate.

Results

Condom use

Predictors in the logistic regression of condom use in the past six months were HIV and ELS status and an HIV/ELS interaction. The logistic regression model was not statistically significant, $\chi 2(4) = 9.08$, $p = 0.059$. The model explained 6.8% of the

variance (Nagelkerke R2) of condom use in the past six months. ELS was not a statistically significant predictor in the model *(B* = -0.89, *SE* = 0.68, Wald =1.72, *p* = .190), neither was HIV *(B* = -0.06, *SE* = 0.52, Wald = 0.01, *p* = .913) and the interaction between ELS and HIV was not significant *(B* = 0.15, *SE* = 0.87, Wald = 0.03, *p* = 0.864). Predictors in the multinomial logistic regression of condom use during lifetime were age, HIV and ELS status and HIV/ELS interaction. The multinomial logistic regression model explained 15.1% of the variance (Nagelkerke R^2) of condom use during lifetime and was statistically significant ($\chi 2(12) = 34.40$, $p = .001$). The model showed that participants reporting using condoms most of the time were more likely to be PWoH with low ELS compared to the other groups *(B* = 1.55, *SE* = 0.76, Wald = 4.15, *p* = 0.042). However, the interaction of ELS and HIV was not significant ($\chi^2(3, n = 231) = 4.81$, $p = 0.186$).

Sex partners

Predictors in the multinomial logistic regression of number of partners in the past six months were age, HIV and ELS status and HIV/ELS interaction. The model explained 26.1% of the variance (Nagelkerke R2) of sex partners in the past six months. Age was a significant predictor but the interaction of ELS and HIV was not a significant predictor in the model ($\chi^2(3, n = 229) = 1.94$, $p = 0.585$). Predictors in the multinomial logistic regression of number of partners during lifetime were age, HIV and ELS status and HIV/ELS interaction. The multinomial logistic regression model was statistically significant ($\chi^2(8) = 18.06$, $p = 0.021$). The model explained 8.5% of the variance (Nagelkerke R2) of sex partners during lifetime. Age was a significant predictor but the interaction of ELS and HIV was not significant in the model ($\chi^2(2, n = 235) = 2.88$, $p = 0.237$).

Hypothesis H2b: Interactive effects of ELS and HIV on IGT and BART

Preliminary Analyses

To meet the linear regression assumption of multivariate normality, outliers (n = 8) were excluded from the BART model. In the subsample with the BART measures without the outliers (n =157), the PWH groups were significantly older (H (3) = 31.70, p<0.001), included more males ($\chi^2(3, n = 157) = 18.62$, $p < 0.001$, Cramer's $V = 0.34$), more likely to self-report past cocaine use ($\chi^2(3, n = 156) = 11.58$, $p = 0.009$, Cramer's $V = 0.27$) and hepatitis B co-infection ($\chi^2(3, n = 157) = 15.10$, p= 0.002, Cramer's $V = 0.31$) (See Table 5). No significant associations were found in the BART score for sex, age, cocaine use or hepatitis B, therefore, no propensity score covariates were included in the model.

Data screening indicated that 27% the of participants with IGT scores (n =124) were missing THC and benzodiazepine urine tox results. Therefore, these variables were not used as covariates as the PWoH/high ELS group would have been reduced to 7 participants. PWH/high ELS group was significantly older (H (3) = 9.35, $p = 0.025$) than the PWoH/low ELS group. The PWH groups with IGT data included more males ($\chi^2(3, n = 124) = 23.31$, $p < 0.001$, Cramer's $V = 0.43$) (see Table 6). Males performed statistically significantly better than females on the IGT task ($t(122) = 2.58$, mean difference = 1.96, $p = 0.011$), as such sex was included as a covariate in the hierarchical multiple regression model.

Results

No interaction between HIV and ELS status was observed on the average number of successful responses (pumps) prior to the popping of the balloons (Adjusted $R^2 = 0.04$,

$p = 0.055$) indicating that PWH with high ELS showed riskier behavior on the BART. No significant main effects were observed for ELS ($\beta = 0.12$, $p = 0.131$) or HIV ($\beta = -0.04$, $p = 0.592$) on the average number of successful responses (pumps) (See Table 7).

HIV and ELS status did not indicate a statically significant interaction on IGT performance (Adjusted $R^2 = 0.06$, $p = 0.519$) (see Table 8). ELS main effect was not statistically significant ($\beta = -0.02$, $p = 0.834$) and no main effect of HIV was observed for the IGT score ($\beta = -0.19$, $p = 0.065$).

Hypothesis H2c: Correlations between brain volumes and sex-risk behavior.

Correlations between brain volumes and IGT, BART, and sex-risk measures (RAB).

Preliminary analyses

In the BART subsample, age was associated with all volumes ($p < 0.05$), cocaine lifetime use was associated with the caudate, parietal lobe, OFC and insula cortex volumes *(*$p < 0.05$) and hepatitis B was associated with caudate, parietal lobe and OFC volumes *(*$p < 0.05$). A propensity score was calculated for these variables. In the IGT subsample, age was associated with all volumes *(*$p < 0.05$) and males performed better on the IGT. Therefore, a propensity score was calculated and included as a covariate in the analyses.

Condom use in the past six months was adjusted to two categories to meet variance assumptions. No covariates were required for the analysis focused on condom use in the past six months. However, condom use lifetime and volumes differed by age, HIV status, alcohol and cocaine lifetime use *(*$p < 0.05$). A propensity score was calculated and included in the ANCOVA models. Number of sex partners in the past six months was adjusted to two categories to meet variance assumptions. Number of sex

partners in the past six months and volumes differed by age and thus age was included as a covariate in one-way ANCOVA models. Number of sex partners during lifetime was reduced to two categories to meet variance assumptions due to group imbalance. Number of sex partners during lifetime and volumes differed by age, alcohol lifetime, HIV status, benzodiazepine urine sample and thus a propensity score was calculated for covariates and was introduced as a covariate in one-way ANCOVA models.

Results

BART

There were no associations between BART performance in the overall sample and volumes of the OFC (r(155) = -.00, p = 0.964), parietal lobe (r(155) = .05, p = 0.511), insula cortex (r(155) = .09, p = 0.238), amygdala (r(155) = .07, p = 0.348), the hippocampus (r(155) = .13, p = 0.110), caudate (r(155) = .06), p = 0.479) and the ACC (r(155) = .07, p = 0.394). There were no significant correlations between BART and brain volumes when groups were divided by HIV status.

IGT

Hippocampal volume was significantly associated with IGT scores in the overall sample (rs (117) = .19, p = 0.039). Specifically, larger hippocampal volume was associated with higher number of advantageous responses after subtraction of less advantageous choices. However, this association did not remain significant after FDR correction. There were no statistically significant associations between IGT score and OFC (r(117) = -.00, p = 0.942), parietal lobe (r(117) = .00, p = 0.973), insula cortex (r(117) = -.04), p = 0.669), amygdala (r(117) = .06, p = 0.483), caudate (r(117) = .07, p =

0.458), and ACC (r(117) = -.05, p = 0.564) volumes. There were no significant correlations between IGT and volumes when groups were divided by HIV status.

Sex-Risk scores (RAB)

Condom use groups (in the past six months) did not differ on volumes in the OFC (t(233) = -1.26, p = 0.209), parietal lobe (t(233) = -1.13, p = 0.260), hippocampus (t(233) = -1.09, p = 0.278), insula cortex (t(233) = -1.00, p = 0.317), amygdala (t(233) = 0.62, p = 0.533), caudate (t(233) = -0.01, p = 0.988) or ACC (t(233)= -1.80, p = 0.074). Furthermore, condom use groups (lifetime) did not differ on brain volumes in the OFC *(F(*3, 221) = 2.44, p = 0.065), parietal lobe *(F* 3, 221) = 2.26, p = 0.065), hippocampus *(F(*3, 226) = 0.33, p = 0. 802), insula cortex *(F(*3, 226) = 0.76, p = 0. 519), amygdala *(F(*3, 226) = 0.30, p = 0.825), caudate *(F(* 3, 221) = 1.44, p = 0.232) or ACC *(F(*3, 226) = 0.73, p = 0.537).

Finally, the groups of number of sex partners (in the past six months) did not differ on brain volumes in the OFC *(F(*1, 232) = 0.00, p = 0.950), parietal lobe *(F(* 1, 232) = 0.38, p = 0.538), hippocampus *(F(*1, 232) = 0.01, p = 0.921), insula cortex (1, 232) = 0.03, p = 0. 865), amygdala *(F(*1, 232) = 1.32 p = 0. 252), caudate *(F*1, 232) = 0.03, p = 0.873) or ACC *(F(*1, 232 = 0.02, p = 0. 897). Number of sex partners groups (lifetime) was reduced to two categories to meet variance assumptions. No statistically significant associations were observed between groups (number of sex partners-lifetime) on brain volumes in the OFC *(F(1*, 230) = 0.05, p = 0. 818), parietal lobe was *(F(1*, 230) = 0.22, p = 0.637), hippocampus *(F(1*, 230) = 3.06, p = 0. 082), insula cortex *(F(1*, 230) = 1.36, p = 0.245), amygdala *(F(*1, 230) = 0.80, p = 0.373), caudate *(F(*1, 230) = 2.62, p = 0.107) or ACC *(F(1*, 230) = 0.88, p = 0.348).

Hypothesis H2d: Moderation model: executive function moderates the relationship between brain volumes and sex-risk behavior.

Preliminary analyses

Sex partners in the last six months was selected as a measure of sex-risk behavior. The distributions of the sex risk groups violated assumptions of multinomial regression. Therefore, groups were collapsed into two categories. The first two categories of lower number of partners were collapsed into one category (79% of participants) and the other two were collapsed into another category (21% of participants). Age *(p'* s < 0.05) was significantly associated with the dependent variable and was included as a covariate in the regression models. The CWIT Trial 3 was selected as the moderator between brain volumes and sex-risk behavior due its association to sex-risk behavior.

Results

Orbitofrontal Cortex

The multivariate logistic regression analysis including the OFC as a region of interest revealed that the models accounted for 8.2% of the variance between brain volumes and number of sex partners in past six months ($\chi^2(4) = 19.35$, $p < 0.001$). Age was a significant predictor of the number of sex partners *(p'*s < 0.05). OFC volume was not a significant predictor of number of sex partners (see Table 9 for complete results). A measure of executive function (CWIT) was not a significant predictor of sex partners in past six months. There was evidence of two-way interaction between OFC volume and CWIT on number of sex partners in past six months *(b* = 0.00, *se* = 0.00, OR = 1.00, *p* = 0.008). Specifically, individuals who performed above average within the sample on the CWIT and had a larger OFC volumes and the number of sex partners in past six months

was lower than individuals with smaller volumes. However, when individuals had a lower than average CWIT score within the sample and a larger OFC the number of sex partners in past six months was higher than individuals with smaller volumes.

Parietal lobe

The multivariate logistic regression analysis including parietal lobe volume as a region of interest revealed that the models accounted for 4.83% of the variance between brain volumes and number of sex partners in the past six months ($\chi^2(4) = 11.38$, p= 0.023). However, only age as a covariate was a significant predictor of the number of sex partners *(p'* s < 0.05). Parietal lobe volume was not a significant predictor of number of sex partners. CWIT was not a significant predictor of sex partners in past six months. There was no evidence of a two-way interaction between parietal lobe volume and CWIT on the number of sex partners in past six months.

Insular cortex

The multivariate logistic regression analysis including the insula cortex volume as a region of interest revealed that the models accounted for 5.10% of the variance between brain volume and number of sex partners in the past six months($\chi^2(4) = 12.02$, $p = 0.017$). However, only the covariate age was a significant predictor of the number of sex partners (p's < 0.05). Insula cortex volume was not a significant predictor of number of sex partners. CWIT was not a significant predictor of sex partners in past six months. There was no evidence of a two-way interaction between insula cortex volume and CWIT on the number of sex partners in past six months.

Amygdala

The multivariate logistic regression analysis including amygdala volume as a region of interest revealed that the models accounted for 4.85% of the variance between amygdala volume and number of sex partners in past six months ($\chi^2(4) = 11.43$, $p = 0.022$). However, only age was a significant predictor of the number of sex partners *(p*s < 0.05). Amygdala volume was not a significant predictor of number of sex partners. CWIT was not a significant predictor of the number of sex partners in past six months. There was no evidence of a two-way interaction between amygdala volume and CWIT on the number of sex partners in past six months.

Caudate

The multivariate logistic regression analysis including caudate volume as a region of interest revealed that the models accounted for 4.19% of the variance between caudate volumes and number of sex partners in past six months ($\chi^2(4) = 9.87$, $p = 0.042$). However, only the covariate age was a significant predictor of the number of sex partners (*p'* s < 0.05). Caudate volume was not a significant predictor of the number of sex partners. CWIT was not a significant predictor of sex partners in past six months. There was no evidence of a two-way interaction between caudate volume and CWIT on the number of sex partners in past six months.

Hippocampus

The multivariate logistic regression analysis including hippocampal volume as a region of interest revealed that the models accounted for 4.43% of the variance between hippocampal volumes and number of sex partners in past six months ($\chi^2(4) = 10.42$, $p = 0.034$). However, only age was a significant predictor of the number of sex partners ($p <$

0.05). Hippocampal volume was not a significant predictor of the number of sex partners. CWIT was not a significant predictor of sex partners in past six months. There was no evidence of a two-way interaction between hippocampal volume and CWIT on the number of sex partners in past six months.

Anterior Cingulate

The multivariate logistic regression analysis including ACC volume as a region of interest revealed that the models accounted for 5.33% of the variance between ACC volumes and number of sex partners in past six months ($\chi^2(4) = 12.57$, $p = 0.014$). However, only age was a significant predictor of the number of sex partners ($p < 0.05$). ACC volume was not a significant predictor of the number of sex partners. CWIT was not a significant predictor of sex partners in the past six months. There was no evidence of a two-way interaction between ACC volume and CWIT on the number of sex partners in past six months.

Unsupervised ML cluster analysis: PWH only

Results

After adjusting parameters of nearest neighbors and minimum distance to better fit the data, UMAP showed an informative 2D data distribution embedding. The embedding defined the dimensions of the data for use of the HDBSCAN algorithm, which subsequently defined the clusters. HDBSCAN delineated three clusters in PWH with a Density Based Clustering Validation of 0.75 -the score ranges from -1 to 1 (Moulavi et al., 2014). The three clusters included 86% of the participants and the rest were regarded as noise (Figure 3). Contrasts between groups demonstrated that the percent of ELS status was statistically significantly different between clusters (see Table

10). Cluster one included participants with low ELS who were more likely to be male, have a lower nadir CD4+ T-cell count, and lower recent and CD4+ T-cell count than participants in cluster three (ps < .05), but no significant differences between participants in cluster one and cluster two on this measures (*p'* s < 0.05). In cluster two, 97% of participants had high ELS, were older with significantly longer duration of infection, lower nadir CD4+ T-cell count, recent CD4+ T-cell count and reported higher lifetime alcohol consumption than cluster one and three (*p'* s < 0.05). Cluster two was significantly older than cluster three and a higher percentage of participants reported using cocaine in the past than cluster one (*p'* s < 0.05). In cluster three, 94% of participants had high ELS.

Comparisons of ELS events by clusters show that participants in cluster two reported more surgery and hospitalizations than the other two clusters. Clusters were similar in executive function. Age correlated with brain volumes and variables of sex risk behavior, but not condom use in the past six months. A propensity score was calculated to include both age and alcohol use for covariate correction as both correlated with parietal lobe and caudate volumes. No differences in volumetric measures were observed after correcting for age and alcohol use when necessary. Age was associated with sex partners during lifetime. Sex partners in the past six months differed by sex. After correcting for age, differences in sex partners during lifetime were shown, however significant differences did not survive FDR corrections. Clusters were similar in condom use and sex partners in previous six months after correcting for age and/or sex (see Table 11).

Discussion

The primary goal of this study was to determine whether ELS interacts with HIV to produce a distinctive pattern of brain structure and function measured by risky behavior. Overall, findings were mixed such that interactive effects of ELS and HIV were detected in structural brain measures, however, no interactive or independent effects of ELS and HIV were detected in risky behavior. Results revealed a differential effect of the interaction between HIV and ELS status on the OFC after multiple comparison corrections in which PWoH/high ELS participants presented larger OFC volumes whereas PWH/high ELS showed smaller volumes on average. Cellularity was significantly higher in the IFOF in PWoH/high ELS than the low ELS groups. ELS did not significantly interact with HIV status on risky behaviors. Executive function moderated the relationship between larger OFC volumes and sex partners in the past six months. Cluster analysis revealed three clusters in PWH that were differentiated by demographic variables only. Although not yet confirmed by research, the susceptibility of the OFC to ELS and HIV might be related to the role of the OFC in emotion regulation, reward and punishment (Golkar et al., 2012; Petrovic et al., 2016). Higher OFC volumes appeared detrimental when associated with lower executive function score or advantageous when associated with higher executive function scores in relation to sex risk behavior. These results indicate the potential for different mechanisms underlying the observed volumetric differences between PWoH/high ELS and PWH/high ELS groups. However, results of the cluster analysis do not indicate that higher ELS is a significant factor identifying unique subgroups of brain or sex risk behavior in PWH.

The hypothesis that HIV infection and history of ELS interact to produce lower brain volume in virally suppressed PWH compared to PWoH with or without ELS was supported. A medium effect size was revealed for the interaction between HIV and ELS on OFC volume, which was associated with smaller volumes for PWH and larger volumes for the PWoH. Consistent with previous findings, PWH show smaller volumes in the OFC, the parietal lobe, insular cortex, caudate and the ACC (Ances et al., 2006; L. M. Baker et al., 2015; J. T. Becker et al., 2012; Behrman-Lay et al., 2016; Sanford et al., 2017). However, ELS status did not exhibit a main effect on volumetric measures between groups. Some studies have found lower volumes in healthy adults with a history of ELS (Andersen et al., 2008; L. M. Baker et al., 2013; Cohen et al., 2006; Korgaonkar et al., 2013), but, other studies have not (Clark et al., 2012; Saleh et al., 2017). Insconsistent results observed in previous studies might be related to variation in genetic makeup (Everaerd et al., 2012; Gupta et al., 2016; Marusak et al., 2016) and/or differences in social determinants of health that modulate ELS effects (Ancelin et al., 2021; Cicchetti, 2010). Furthermore, lower volumes in PWH/high ELS might reflect a higher impact of stressors across the lifespan. For example, an HIV diagnosis has been reported in other studies to be a substantial psychological stressor (Hosek et al., 2018; Huang et al., 2020) and biological stressor (Doitsh et al., 2014). The OFC might be vulnerable to the effects of ELS due to its role in emotion regulation where it modulates threat reponses from the amygdala during stressful events throughout lifetime.

The larger brain volumes observed in PWoH/high ELS participants is an unexpected finding. Average or larger OFC volumes in the presence of high ELS have been associated with resilience in previous research. For example, Saleh (2017) reported

that ELS exposure was associated with larger OFC volumes in participants with no depression history, but smaller OFC volumes were observed among individuals with recurrent Major Depressive Disorder. The participants in this study did not have active psychiatric conditions in either the PWH nor PWoH groups. A larger OFC has been associated with reappraisal -the reinterpretation of an emotionally charged situation by changing the meaning and reducing the emotional burden (Welborn et al., 2009), increased optimism, and reduced anxiety in healthy adults (Dolcos et al., 2016). The OFC is involved in processing social–emotional information (Bramham et al., 2009), and forming associations of positive and negative reinforcements (Shott et al., 2015) through connections with the amygdala. However, Clark & colleagues (2012) reported larger amydala volumes among PWH who had a history of ELS, which might be associated with higher symptoms of depression in the PWH/high ELS group. Larger OFC volumes have been related to both adaptive strategies such as reappraisal, but also to impulsivity traits in psychopathic individuals (Ermer et al., 2013; Korponay et al., 2017). More studies are needed examining OFC volumes and different cognitive functions related to emotions.

Smaller volumes associated with ELS in healthy individuals might be related with the presence or history of psychiatric symptoms. Kim et al. (2019) reported that the association between higher ELS and higher trait anxiety was reduced by greater thickness of the OFC. Furthermore, a longitudinal study found that OFC thickness in healthy individuals with ELS was inversely related to depressive symptoms (Monninger et al., 2020). In the present study, even in controlled HIV without psychiatric comorbidities, PWH/high ELS had significantly smaller OFC volumes than PWH/low ELS, which

supports findings of previous ELS/HIV studies (Thames et al., 2018; Clark et al., 2018). Future functional imaging studies could help elucidate the role of the OFC on specific strategies of emotion regulation among PWH with a history of ELS. The inclusion of post-traumatic stress symptoms and resilience measures (Boldrini et al., 2019; Espinoza Oyarce et al., 2020; Schmaal et al., 2016) might help clarify the inconsistency in findings between this study and other similar research.

An interaction between HIV and ELS was detected in cellularity of the fronto-occipital fasciculus that survived multiple comparison corrections. However, DBSI cellularity was significantly higher in the IFOF in PWoH/high ELS compared to participants in the other groups and no independent effecs of HIV nor ELS were observed. The higher cellularity in PWoH on the IFOF is supported by previous DTI research which detected lower fractional anysotropy in the IFOF in healthy adults who reported ELS (McCarthy-Jones et al., 2018; Tendolkar et al., 2018). These outcomes have been confirmed by longitudinal studies showing increased peripheral blood markers of inflammation in adults who experienced ELS (Bourassa et al., 2021; Kuzminskaite et al., 2020; Crick et al., 2022). Additionally, a meta-analysis of cytokine levels in the brain revealed that ELS induces increased proinflammatory cytokines such as IL-1β, IL-6, and TNF-α in the rodent brain in areas such as the hippocampus and prefrontal cortex in younger animals (Lumertz., et al 2022). The higher inflammation marker detected in the IFOF in PWoH with high ELS might correspond to larger volumes in the OFC in this group. The IFOF connects the OFC to subcortical and cortical areas in the temporal and occipital lobe. Larger OFC volumes in PWoH/high ELS might reflect higher inflammation. Longitudinal studies are needed to compare the effects of ELS on

neurostructural measures and neuroinflammatory markers in different stages of the lifespan.

The lack of group differences in cellularity among PWH may be explained by multiple factors. For example, neuroinflammation can be influenced by ART adherence and viral suppression. A previous study revealed no associations between cellularity and HIV-related clinical laboratory measures or neuropsychological variables (Strain et al., 2017). In the same study, higher whole brain cellularity was observed in PWH compared to PWoH; however, cellularity was moderated by ART duration (Strain et al., 2017). Other research has related lower viral load to lower levels of peripheral inflammation in PWH, yet levels were not similar to PWoH (Hileman & Funderburg et al., 2017), but not all studies have reported this finding (Boerwinkle et al., 2020). Neuroinflammation in the brain can be influenced by a myriad of factors, such as cardiovascular disease (Thackeray et al., 2018), diabetes (Van Dyken & Lacoste, 2018) and food intolerances (L. Zhou et al., 2019), that were not available for analysis in the present study. However, these factors might have influenced the DBSI outcomes in the present study and should be included in future studies.

The hypothesis that ELS interacts with HIV on sex-risk behaviors in virally suppressed PWH was not supported. Although the overall model was not significant, results of this study show that participants without ELS or HIV report using condoms most of the time, which supports the hypothesis that PWoH with low ELS and are less likely to engage in risky behaviors such as having unprotected sex. The lack of significant results between groups might be due to the unique population that was included in the study. The exclusion of participants with current problematic substance

use and other co-infections that are also associated with risky behavior might have resulted in an overall sample with less risky behaviors. The PWH sample had high adherence to ART, which was demonstrated by their undetectable viral loads, indicating that the participants were better able to take care of their overall health. Medication adherence is considered to fall within the health/safety domain of risky behaviors along with sexual behavior and substance use (Blais & Weber, 2006; Remien et al., 2014; Suonpera et al., 2020). Some PWH in this study have participated in research studies for several years, which might indicate interest in health-seeking behaviors vs. engagement in and risky behaviors. Participation in research and exposure to knowledge about how to reduce risky behaviors might explain the lack of differences in sex risk behaviors between PWH and controls. Other factors, such as self-esteem, have been related to sex risk behavior (MacDonald & Martineau, 2002; Moulier et al., 2019). Self-esteem might be an important measure to include in future studies as this could be associated with increased variability in risky behavior.

The hypothesis that ELS interacts with HIV on risky decision-making tasks in virally suppressed PWH was not supported. There were no significant interactions between HIV and ELS in risky behaviors measured by BART and IGT. No interaction was observed on the BART and no effects of ELS on either BART or IGT performance were observed. HIV status was not a significant predictor of performance on the BART or the IGT. The results of the IGT and BART support the results of other studies that did not find differences on IGT or BART by HIV status (Iudicello et al., 2013; Vassileva et al., 2013). However, other studies have demonstrated higher risky behaviors on IGT in PWH (Smith et al., 2018; Thames et al., 2012). Differences in the studies outcomes might

be related to different treatment status of the samples. For example, in the Smith et al., (2018) study, the participants were young adults, not all participants were on ART and 51% had an undetectable viral load. Furthermore, in Thames et al., (2012) only 33% of the PWH had an undetectable viral load. In this study, only PWH with an HIV suppressed viral load were included which could have resulted in a sample with less risky behaviors.

Laboratory paradigms that assess risky behavior such as the IGT and BART were developed to predict real world behaviors including sex-risk behaviors (Bechara et al., 1994; Lejuez et al., 2002), but the relevance of these measures to real-world (sex-risk) behaviors has been inconsistent (Golub et al., 2016; Kim et al., 2018; Reynolds et al., 2019). The limited success using a decision-making laboratory financial approach (e.g., IGT and BART) to predict behaviors in a health domain such as sex-risk behaviors might be related to a limited overlap between brain systems involved in financial-reward risk-taking tasks and sexual behavior (Hagen et al., 2016; Iudicello et al., 2013; Rendina et al., 2018). The overlap between brain systems of different types of risky behaviors might be more difficult to capture when an actual financial reward is not provided. Monetary risk-taking tasks may not adequately capture all aspects of risk-taking behavior, particularly the health aspects that are often compromised in PWH (Gilman et al., 2015; Kim et al., 2018). Thus, in this study, sex-risk measures of risk-taking behaviors were included to complement monetary risk-taking tasks.

The hypothesis that lower brain volumes will be associated with increased self-report of sex-risk behavior, and worse performance on the BART and IGT in PWH and ELS was not supported. Hippocampal volume was associated with the IGT score,

however, the effect size was small and did not survive multiple comparisons corrections. Although, some lesion studies have associated the OFC or ventromedial prefrontal cortex to risky behavior on the IGT (Bechara et al., 1994, 1999, 2000), recent studies have associated the IGT with damage or reduced volumes in other regions of the frontal lobe such as lateral prefrontal cortex (Fogleman et al., 2017), superior medial frontal volumes (Fujiwara et al., 2008) and dorsolateral prefrontal cortex (Ouerchefani et al., 2017). Neuroimaging findings that associate the IGT to different prefrontal areas map onto the main cognitive functions related to the IGT such as problem-solving and attentional skills (Gansler et al., 2011), which might indicate a more prominent role of the above mentioned areas associated with problem-solving and attentional skills involved in risky decision-making tasks.

No relationship between brain volumes and the BART was observed. This result is in accordance with another study that only found associations of the BART to the anterior insula (Nasiriavanaki et al., 2015). The present study did not investigate the partitions of the insula, which might explain discrepancies in the results with previous research. Furthermore, no relationship between volumes and sex risk behavior was observed. A large study demonstrated associations of reduced volumes in the hippocampus, amygdala, insula and ventro-medial prefrontal cortex and higher risk behaviors defined as how likely are individuals to engage in risky decisions associated with their own health (Aydogan et al., 2021). In the subsample of participants who completed the BART, hepatitis B was associated with smaller volumes in the caudate, parietal lobe and the OFC. Smaller brain volumes have been linked with cirrhosis (Lu et al., 2018), as such, a history of hepatitis B might have an impact in brain morphometry.

Cocaine use was inversely associated with volumes of the caudate, parietal lobe, OFC and insula cortex which has been supported by other studies (Ersche et al., 2011; Hanlon et al., 2011). Different study results might be related to the inclusion of different risky behaviors such as alcohol consumption, smoking and fast driving along with number of sexual partners.

The hypothesis that executive function would moderate the relationship between brain volumes and sex-risk behavior was supported. OFC volume and CWIT performance were not significant independent predictors of number of sex partners. However, the OFC volume and CWIT performance associated with the number of sex partners in past six months. Whether larger OFC volumes were advantageous or detrimental in relation to sex risk behavior was dependent on the performance on the CWIT as a measure of executive function. Larger OFC volume was associated with lower sex risk behavior only when performance on the CWIT was higher than the average performance of the sample. However, when larger OFC volume was associated with poorer performance on the CWIT, participants reported higher sex risk behavior.

Whether larger volumes on the OFC indicate bether performance is unclear. There are several reasons why the OFC can be larger. For example, larger OFC in participants who performed better on the CWIT might reflect compensation mechanisms, whereas larger OFC in participants that performed worse than average might indicate lack of pruning in development. The OFC is involved in monitoring past success and failure outcomes to update behavior for future trials in the CWIT (Verstynen, 2014). The OFC connects with dorsolateral prefrontal cortex and middle frontal gyrus, which reduced volumes have been associated with poor performance on the CWIT and adjustment of

reward values (Adólfsdóttir et al., 2014; Heflin et al., 2011; Staudinger et al., 2011). A cognitive strategy known to modulate risky behavior is reappraisal (Braunstein et al., 2014). Reappraisal has been found to reduce CWIT interference when induced in sad mood (Keng et al., 2017). The OFC is related to processing social reward and punishment such as tendency to shift personal preferences for another persons preferences (Campbell-Meiklejohn et al., 2012) and facial expression recognition (Tsuchida & Fellows, 2012). Given that sex risk behaviors involve many processes related to emotions and social interactions, the OFC might be related to sex risk behaviors as part of a network of brain areas associated to executive function captured by the CWIT. OFC volume and sex risk behavior have been associated with the CWIT (Verstynen et al., 2014; Yuan et al., 2015; Fatima et al., 2019), which measures selective attention, cognitive flexibility and response inhibition.

The lack of a direct relationship between the OFC and the CWIT might be due to the lack of sensitivity of the CWIT to detect complex real-world processes. These results elucidate the need to contrast volumetric measures with cognitive measures as larger volumes might be related to beneficial (e.g., compensation) but also detrimental processes (e.g., lack of pruning or inflammation). Furthermore, different areas of the OFC have been related to different cognitive processes. For example, the medial OFC has been associated with reward value and the lateral OFC with self-monitoring and punishment (Rolls et al., 2020). Because different areas of the OFC have been associated to different functions, the possibility persists that the lateral OFC was related to the CWIT and the medial OFC was related to social reward and therefore only an interaction

between OFC, CWIT and sex risk behavior was observed. Studies are needed to examine how the OFC subdivisions relate to executive function and sex risk behavior.

The hierarchical clustering algorithm detected three clusters that grouped PWH by ELS status and HIV clinical variables. Among the two clusters (cluster 2 and 3) with high ELS status, differences were observed on clinical variables and substance use. On average, participants in cluster two were older than cluster three, which was associated with duration of infection. No differences were detected on brain volumes or sex risk behavior after correcting for demographic variables which ultimately indicates that ELS was not associated with subgroups with different brain and behavioral outcomes. Differences detected in HIV clinical variables between clusters two and three might be related to unmeasured social determinants of health. Recent research has demonstrated the impact of these factors on health in PWH (Wisch et al., 2022). Although the ELSQ includes a question of poverty, natural disaster, house destroyed, and bullying, other measures of social determinants of health such as safety of neighboorhood, racism, discrimination, pollution of environment among others were not measured but are known determinants in the area where this study took place. The mentioned factors can also have a great impact in brain and behavioral development (Thames et al., 2018; Cserbik et al., 2020). Overall, the clustering results did not support the exploratory aim 1. The clutering analysis suggest that high ELS does not contribute to the designation of clinically relevant diverse clusters in virological suppressed PWH without psychiatric comorbidities.

These findings must be interpreted with caution, however, since this present study was a cross-sectional study and history of anxiety or history of Major Depressive

Disorder was not evaluated. Only current symptoms of Major Depressive Disorder was used as an exclusion criterion. Although an attempt was made to include a sample that was free from confounds identified in prior studies, the present work has pointed to other potential confounds that were not included. Stressors during development can be challenging to ascertain because of the use of retrospective reporting (Colman et al., 2015). Further, this study did not assess age or duration of exposure to each ELS. Chronic exposure to ELS events may alter and possibly eliminate biological differences between events. As such, additional studies are needed to examine the interaction between timing and duration of exposure to ELS events and HIV infection, as well as understanding biological and social stressors experienced in adulthood. Cellularity measured by DBSI is an indirect measure of brain inflammation, which might be influenced by immune activation factors not related to HIV or ELS. Direct markers of inflammation were not available for analysis to elucidate immunological correlates of HIV and ELS. Additionally, high angular resolution diffusion imaging (HARDI) has been recently developed that might be more accurate in detecting low grade chronic neuroinflammation (Yik et al., 2022). Furthermore, our sample consisted of healthy individuals who report experiencing childhood trauma yet do not report current psychiatric disorders. As such, this sample may represent a resilient population. The broader exclusion criteria might have resulted in a sample that did not characterize the general ELS phenotype that include higher psychological distress and substance abuse. Additionally, the PWH groups were significantly older with more time with the disease, which migh have influenced the results. Lastly, the current study is a cross-sectional research design and therefore

trajectories of brain integrity associated to the effects of HIV and ELS could not be examined.

Collectively, the study results indicate an impact of high ELS in virologically well controlled PWH and PWoH. High ELS is associated with structural abnormalities in the OFC in both PWH and PWoH with high ELS compared to low ELS groups, however, in different directions. OFC differences in PWH/high ELS suggest that ELS may increase vulnerability to effects of HIV in the brain. No interactions were found between ELS and HIV measures of risky behavior. The current study included a relatively healthy cohort of participants despite ELS, with no current mental health comorbidity, and PWH were medication adherent. Although no direct associations of OFC volumes and executive function with sex risk behavior were detected, the results of the study indicate executive function is an important moderator between higher volumes in the OFC and sex risk behavior.

These results underline the importance of cognitive measures to determine associations between volumetric measures and behavioral measures as relationships might be indirect among PWH with ELS who have relatively few comorbidities. Hierarchical clustering detected clusters in PWH defined by demographic and HIV clinical variables only, which suggests that different volumetric and behavioral outcomes associated with ELS might be related to an interplay between ELS and other factors such as substance use and social determinants of health. Results from the current study support previous findings detecting smaller volumes in PWH/high ELS groups compared to PWoH and PWH/low ELS. However, ELS direct impact on executive function and risky behavior was undetectable without the effects of other factors. New studies should focus

on the potential negative effects of substance use when use patterns are subclinical in severity. Future research should identify intervention strategies aimed at enhancing resilience and coping strategies that would mitigate and might even reverse the effects of ELS on brain neurostructure in healthy participants and in PWH.

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Figure 1

The Adverse Childhood Experiences Framework of the CDC-Kaiser Permanente Adverse Childhood Experiences Study (CDC, 2020a).

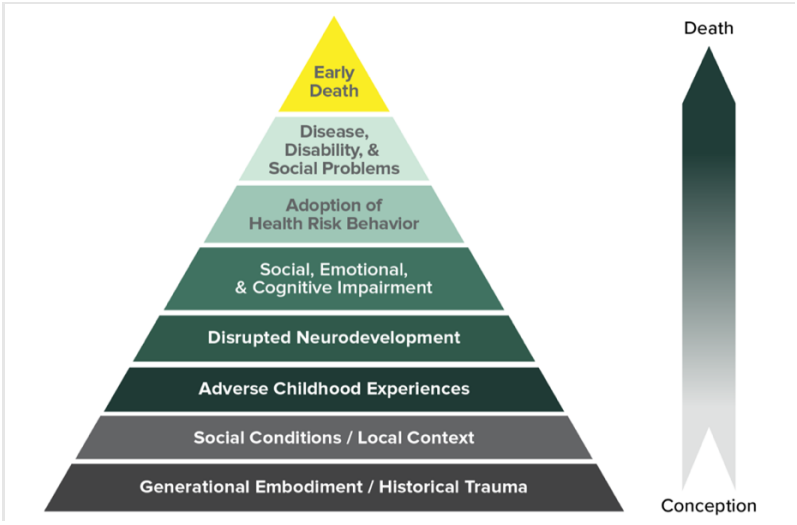


Figure 2

Conceptual Diagram of the Model to Analyze Interaction Effects in Sex-Risk Behavior Allowing a Moderation Effect.

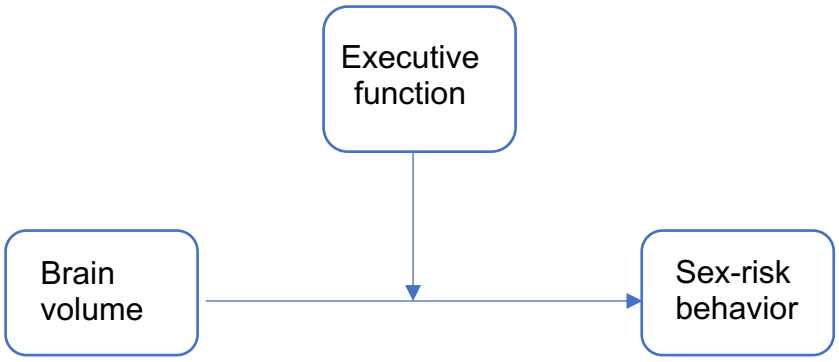


Table 1.

Demographic Characteristics of the Volumes and Sex Risk Sample

	PWoH/low ELS (n=57)	PWoH/high ELS (n=56)	PWH/low ELS (n=43)	PWH/high ELS (n=79)	*p*
Med age (yrs.) (IQR)	37.0 (33.5)	24.5 (27.0)	55.0 (14.0)	55.0 (13.0)	<0.001*
% Males	53%	43%	81%	71%	<0.001*
Mean education (yrs.) (SD)	13.7 (2.0)	13.5 (1.8)	13.9 (2.8)	13.5 (2.7)	0.830
Mean WRAT-3 (SD)	46.6 (7.6)	46.2 (7.4)	44.8 (9.6)	44.2 (9.1)	0.356
Ethnicity %					0.617
African American	49%	52%/	63%	58%	
White	49%	46%	37%	38%	
Other	2%	2%	0%	4%	
Mean BDI-II (SD)	5.7 (6.3)	7.6 (7.5)	7.9 (7.4)	10.0 (7.3)	0.006*
Mean ELS events (SD)	1.0 (0.8)	5.1 (2.2)	1.1 (0.8)	5.1 (2.0)	<0.001*
Mean months of infection duration (SD)			175.4 (103.4)	195.5 (113.3)	0.337
Mean recent CD4 count, cells/μL (SD)			633.8 (304.3)	610.1 (286.9)	0.670
Mean nadir CD4 count, cells/μL (SD)			234.6 (202.4)	197.2 (205.5)	0.362
Viral load undetectable (%)			100%	100%	1.000
Substance use KMSK lifetime					
Med Alcohol score (IQR)	8.0 (7.0)	7.0 (7.0)	8.0 (7.0)	9.0 (7.0)	0.318
Med Tobacco score (IQR)	3.0 (10.5)	2.0 (9.0)	7.0 (10.0)	9.0 (11.0)	0.135
Cocaine (% yes)	14%	11%	33%	40%	<0.001*
Opiates (% yes)	2%	4%	2%	4%	0.883
Utox THC (% +)	23%	36%	44%	51%	0.009*
Utox Benzodiazepine (% +)	2%	2%	9 %	16%	0.014*
Infection history					
Hepatitis A (% +)	0%	2 %	5%	11%	0.001*
Hepatitis B (% +)	0%	0%	16%	23%	<0.001*
Tuberculosis (% +)	0%	0%	8%	9%	0.015*

Note. *Significant difference between groups $p < 0.05$; WRAT-3 = The Wide Range Achievement Test 3; BDI-II = Beck Depression Inventory-II; KMSK = Kreek-McHugh-Schluger-Kellogg scale; Utox = Urine Toxicology Screen; THC = Tetrahydrocannabinol.

Table 2.

Independent and Interactive Effects of HIV/ELS on Brain Volumes in Adjusted Analyses

	Orbitofrontal Cortex				Parietal Lobes				Insula Cortex			
	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE
Step 1	0.01	2.29			0	0.3			0.14***	38.87		
PS			1234.01	815.18			2019.73	3714.46			-24.45***	3.92
Step 2	**0.14****	**19.22**			0.15***	19.91			0.02	2.34		
PS			850.81	761.61			-245.68	3470.64			-23.08***	4.36
HIV			**-786.90****	**127.01**			-3678.12***	589.55			-44.92	70.44
ELS			135.25	113.67			1007.97	528.3			-109.25	56.39
Step 3	**0.03****	**8.43**			0.01	3.78			0	0.1		
PS			1137.21	755.75			177.74	3456.13			-22.94***	4.39
HIV			**-785.20****	**124.96**			-3678.04***	585.92			-45.88	70.65
ELS			128.54	111.86			992.42	525.11			-109.15	56.5
HIVxELS			**-271.93****	**93.67**			-847.98	435.93			-14.91	47.27

Note. Significant at $*p < 0.05$, $**p = < 0.01$, $***p = < 0.001$, bolded *p* values when overall regression model survived FDR correction; PS = Propensity score

Table 2. (Cont.)

Independent and Interactive Effects of HIV/ELS on Brain volumes when Controlling for Covariates

	Caudate				Amygdala				Hippocampus				Anterior Cingulate			
	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE
Step 1	0	0.33			0.05***	11.56			0.04***	10.39			0.05***	11.56		
PS			-206.16	358.86			-4.56***	1.34			-9.59***	2.97			-4.50***	1.34
Step 2	0.13***	17.5			0.02	2.87			0.01	1.43			0.02	2.87		
PS			-322.01	337.49			-3.20***	1.48			-7.16***	3.32			-3.20*	1.48
HIV			-325.50***	56.28			-47.71	24.01			-86.36	53.62			-47.71*	24.01
ELS			-17.24	50.374			-19.1	19.22			-10.42	42.93			-19.09	19.22
Step 3	0	0.01			0	0.03			0	0.18			0	0.03		
PS			-326.73	341.16			-3.23***	1.5			-7.29***	3.34			-3.23*	1.5
HIV			-325.53***	56.41			-47.53	24.08			-85.38	53.8			-47.53*	24.08
ELS			-17.12	50.5			-19.11	19.26			-10.52	43			-19.1	19.26
HIVxELS			4.51	42.28			2.83	16.11			15.18	35.98			2.83	16.11

Note. Significant at *$p < 0.05$, **$p = < 0.01$, ***$p = < 0.001$, bolded p values when overall regression model survived FDR correction; PS = Propensity score

Table 3.

Demographic Characteristics of the Subsample who Completed Diffusion Basis Spectrum Imaging

	PWoH/low ELS (n=30)	PWoH/high ELS (n=29)	PWH/low ELS (n=32)	PWH/high ELS (n=57)	*p*
Med age (yrs.) (IQR)	23.0 (19.5)	23.0 (15.0)	55.0 (17.7)	54.0 (19.5)	<0.001*
% Males	50%	41%	84%	75 %	<0.001*
Mean education (yrs.) (SD)	13.7 (2.3)	13.5 (1.7)	13.7 (2.5)	13.7 (2.9)	0.945
Ethnicity %					0.125
African American	33%	48%	72%	47%	
White	63%	48%	28%	46%	
Other	4%	4%	0%	7%	
Mean BDI-II (SD)	5.2 (7.0)	8.0 (6.1)	7.6 (7.1)	10.6 (7.9)	0.008*
Mean ELS events (SD)	1.2 (0.7)	5.1 (2.0)	1.1 (0.9)	5.3 (2.0)	<0.001*
Mean months of infection duration (SD)			158.7 (106.0)	180.0 (116.3)	0.439
Med recent CD4 count, cells/μL (IQR)			675.0 (296.2)	555.0 (459.0)	0.915
Med nadir CD4 count, cells/μL (IQR)			200.0 (325.2)	154.0 (275.0)	0.298
Viral load undetectable (%)			100%	100%	1.000
Substance use KMSK lifetime					
Mean Alcohol score (SD)	7.2 (3.6)	6.4 (3.7)	7.2 (3.8)	7.8 (3.8)	0.529
Med Tobacco score (IQR)	2.0 (9.5)	2.0 (4.6)	4.5 (10.0)	9.0 (11.0)	0.629
Cocaine (% yes)	13%	4%	38%	40%	<0.001*
Opiates (% yes)	3%	4%	0%	4%	0.763
Utox THC (% +)	40 %	52%	53%	46%	0.713
Utox Benzodiazepine (% +)	3%	0%	6 %	11%	0.157
Infection history					
Hepatitis A (% +)	0%	3 %	0%	11%	0.059
Hepatitis B (% +)	0%	0%	16%	21%	0.004*
Tuberculosis (% +)	0%	0%	13%	9%	0.077

Note. *Significant difference between groups $p < 0.05$; BDI-II = Beck Depression Inventory-II; KMSK = Kreek-McHugh-Schluger-Kellogg scale; Utox = Urine Toxicology Screen; THC = Tetrahydrocannabinol.

Table 4.

Independent and Interactive Effects of HIV/ELS on DBSI Measures.

	Inferior fronto-occipital Fasciculus				Superior Longitudinal Fasciculus				Cingulum				Anterior Corpus Callosum			
	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE	ΔR^2	ΔF	B	SE
Step 1	0.00	0.13			0.00	0.22			0.01	0.45			0.00	0.650		
HIV			0.00	0.00			0.00	0.00			0.00	0.00			0.00	0.00
ELS			0.00	0.00			-0.00	0.00			0.00	0.00			0.00	0.00
Step 3	**0.05****	**8.16**			0.02	3.44			0.03	4.12			0.01	1.01		
HIV			0.00	0.00			0.00	0.00			0.00	0.00			0.00	0.00
ELS			0.00	0.00			-0.00	0.00			0.00	0.00			0.00	0.00
HIVxELS			**-0.00****	**0.00**			-0.00	0.00			-0.00	0.00			-0.00	0.00

Note. Significant at *$p < 0.05$, **$p = < 0.01$, ***$p = < 0.001$, bolded p values when overall regression model survived FDR correction.

Table 5.

Demographic Characteristics of Sample who Completed the Balloon Analogue Risk Task

	PWoH/low ELS (n=30)	PWoH/high ELS (n=46)	PWH/low ELS (n=29)	PWH/high ELS (n=52)	*p*
Med age (yrs.) (IQR)	31.0 (24.5)	24.5 (22.7)	51.0 (22.0)	51.0 (19.2)	<0.001*
% Males	50%	43%	79%	79 %	<0.001*
Mean education (yrs.) (SD)	13.4 (2.1)	13.3 (1.6)	13.8 (2.7)	13.2 (2.7)	0.801
Ethnicity %					0.428
African American	47%	50%	69%	56%	
White	53%	46%	32%	42%	
Other	0%	4%	0%	2%	
Mean BDI-II (SD)	6.2 (5.7)	8.5 (7.5)	8.9 (7.6)	10.6 (7.2)	0.065
Mean ELS events (SD)	1.4 (0.7)	5.3 (2.1)	0.8 (0.8)	4.7 (1.9)	<0.001*
Mean months of infection duration (SD)			156.9 (93.2)	185.8 (113.4)	0.248
Mean recent CD4 count, cells/μL (SD)			627.5 (323.9)	636.2 (323.3)	0.908
Mean nadir CD4 count, cells/μL (SD)			254.9 (210.6)	190.1 (180.4)	0.156
Viral load undetectable (%)			100%	100%	1.000
Substance use KMSK lifetime					
Med Alcohol score (IQR)	6.5 (7.2)	6.6 (7.2)	7.0 (6.5)	9.0 (7.0)	0.450
Med Tobacco score (IQR)	2.0 (5.3)	4.6 (9.0)	0.0 (10.5)	8.0 (11.0)	0.479
Cocaine (% yes)	10%	9%	24%	33%	0.009*
Opiates (% yes)	7%	4%	7%	4%	0.925
Utox THC (% +)	50%	52%	58%	60%	0.791
Utox Benzodiazepine (% +)	7%	2%	3 %	12%	0.250
Infection history					
Hepatitis A (% +)	0%	2 %	14%	10%	0.072
Hepatitis B (% +)	0%	0%	14%	19%	0.002*
Tuberculosis (% +)	0%	0%	0%	10%	1.000

Note. *Significant difference between groups $p < 0.05$; BDI-II = Beck Depression Inventory II; KMSK = Kreek-McHugh-Schluger-Kellogg scale; Utox = Urine Toxicology Screen; THC = Tetrahydrocannabinol.

Table 6.

Demographic Characteristics of Sample with Iowa Gambling Task Measure

	PWoH/low ELS (n=32)	PWoH/high ELS (n=16)	PWH/low ELS (n=29)	PWH/high ELS (n=46)	p
Med age (yrs.) (IQR)	34.0 (34.5)	36.0 (35.2)	57.0 (19.5)	51.0 (34.0)	0.025*
% Males	48%	37%	96%	72 %	<0.001*
Mean education (yrs.) (SD)	13.4 (2.1)	14.1 (2.3)	14.1 (2.5)	13.6 (2.2)	0.550
Ethnicity %					0.762
African American	55%	69%	69%	63%	
White	42%	31%	31%	35%	
Other	3%	0%	0%	2%	
Mean BDI-II (SD)	7.0 (6.6)	7.6 (7.6)	8.1 (8.9)	11.4 (7.7)	0.055
Mean ELS events (SD)	0.9 (0.8)	5.5 (2.8)	0.9 (0.7)	5.4 (2.1)	<0.001*
Med months of infection duration (IQR)			145.0 (179.5)	146.0 (242.0)	0.934
Mean recent CD4 count, cells/μL (SD)			584.7 (186.0)	616.7(308.8)	0.577
Mean nadir CD4 count, cells/μL (SD)			200.2 (169.5)	203.1 (185.2)	0.948
Viral load undetectable (%)			100%	100%	1.000
Substance use KMSK lifetime					
Med Alcohol score (IQR)	7.0 (5.0)	3.0 (5.0)	7.0 (7.0)	6.0 (7.0)	0.423
Med Tobacco score (IQR)	2.5 (10.7)	0.0 (7.2)	0.0 (10.0)	7.0 (11.0)	0.103
Cocaine (% yes)	12%	6%	39%	39%	0.100
Opiates (% yes)	0%	6%	4%	2%	0.586
Infection history					
Hepatitis A (% +)	0%	0%	11%	7%	0.191
Hepatitis B (% +)	0%	0%	14%	11%	0.086
Tuberculosis (% +)	0%	0%	11%	4%	0.159

Note. *Significant difference between groups $p < 0.05$; BDI-II = Beck Depression Inventory-II; KMSK = Kreek-McHugh-Schluger-Kellogg scale.

Table 7.

Independent and Interactive Effects of HIV/ELS on Balloon Analogue Risk Task score.

			Mean Adjusted pumps	
	ΔR^2	ΔF	B	SE
Step 1	0.02	1.27		
HIV			-0.14	0.27
ELS			0.34	0.22
Step 2	0.02	3.73		
HIV			-0.14	0.27
ELS			0.36	0.22
HIVxELS			0.38	0.20

Note. Significant at *$p < 0.05$, **$p = < 0.01$, ***$p = <$ 0.001, bolded *p* values when overall regression model survived FDR correction.

Table 8.

Independent and Interactive Effects of HIV/ELS

on Iowa Gambling Task Adjusted Score when Controlling for Sex

	Advantageous Cards Minus Disadvantageous Cards			
	ΔR^2	ΔF	B	SE
Step 1	-0.052**	6.66		
Sex			-1.96*	0.76
Step 2	-0.03	2.14		
Sex			-2.56**	0.83
HIV			-0.61	0.06
ELS			-0.02	0.83
Step 3	-0.00	0.42		
Sex			-2.60+	0.83
HIV			-0.62	0.33
ELS			-0.07	0.34
HIVxELS			0.14	0.22

Note. Significant at *$p < 0.05$, **$p = < 0.01$, ***$p = < 0.001$, bolded p values when overall regression model survived FDR correction.

9.

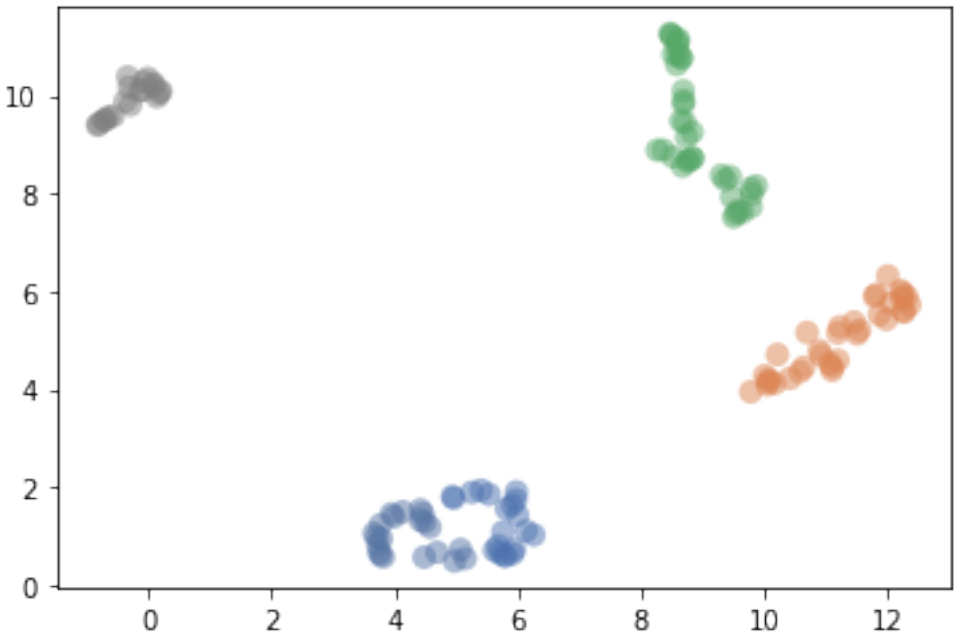
Models of the Effect of Brain Volumes on Number of Sex Partners in the Past Six Months Moderated by the Color Word Interference Task

Predictor	Beta	SE	95% CI	
OFC cm^3	.0001	.0001	-.0001	.0003
CWI3	.0144	.0102	-.0068	.0356
OFC x CWIT	**.0000****	**.0000**	**.0000**	**.0000**
Age	**-.0377***	**.0140**	**-.0610**	**-.0063**
Parietal lobe cm^3	.0000	.0000	.0000	.0001
CWI3	.0132	.0097	-.0059	.0323
Parietal x CWIT	.0000	.0000	.0000	.0000
Age	-.0255*	.0128	-.0506	-.0003
Insula cortex cm^3	.0001	.0002	-.0002	.0005
CWI3	.0072	.0099	-.0122	.0266
Insula x CWIT	.0000	.0000	.0000	.0000
Age	-.0283*	.0116	-.0510	-.0056
ACC cm^3	.0002	.0003	-.0004	.0007
CWI3	.0082	.0097	-.0108	.0273
ACC x CWIT	.0000	.0000	.0000	.0001
Age	-.0315**	0.0116	-.0543	-.0087
Caudate cm^3	.0001	.0002	-.0004	.0005
CWI3	.0108	.0093	-.0075	.0291
Caudate x CWIT	.0000	.0000	.0000	.0000
Age	-.0319**	.0122	-.0558	-.0080
AMG cm^3	-.0005	.0005	-.0015	.0006
CWI3	.0114	.0095	-.0097	.0274
AMG x CWIT	.0000	.0000	.0000	.0001
Age	-.0340**	.0111	-.0556	-.0123
HPC cm^3	.0001	.0002	-.0004	.0005
CWI3	.0143	.0098	-.0049	.0335
HPC x CWIT	.0000	.0000	.0000	.0000
Age	-.0307**	.0110	-.0523	-.0091

Note. Significant at *$p < 0.05$, **$p = < 0.01$, ***$p = < 0.001$, bolded p values when overall regression model survived FDR correction; CWIT = Color Word Interference Test; OFC= Orbitofrontal cortex; HPC = Hippocampus; ACC =Anterior Cingulate; AMG =Amygdala

Figure 3.

Hierarchical Density-Based Spatial Clusters



Note. The results of the hierarchical clustering analysis depicts three cluster and noise. Cluster one depicted in blue dots, cluster two depicted in orange, cluster three depicted in green and non-clustered outliers in gray. X and Y axis represent core distances mapped into 2D plane in which every dot represents a participant. The clusters were defined by HIV related clinical variables (duration of infection, recent CD4+ T-cell count, nadir CD4+ T-cell count) and high/low early life events of the PLW sub-sample.

Table 10.

Demographic Characteristics by Cluster Groups of PLW

	Cluster 1 (n=39)	Cluster 2 (n=34)	Cluster 3 (n=32)	*Test*	*p*
Mean age (yrs.) (IQR)	51.3 (12.5)	56.0 (7.74)	50.6 (12.5)	$F = 3.2$	0.047*
% Males	87%	73.5 %	56.2%	$\chi^2 = 8.6$	0.014*
Mean education (yrs.) (SD)	14.0 (2.7)	13.4 (3.2)	13.3 (2.6)	$F = 0.7$	0.506
Ethnicity %				$\chi^2 = 6.3$	0.386
African American	61.5%	47%	62.5%		
White	38.5%	50%	34.5%		
Other	0%	3%	3%		
ELS status (% high)	0%	97%	94%	$\chi^2 = 93.1$	<0.001*
Mean BDI-II (SD)	7.4 (7.6)	9.7 (7.4)	10.7 (7.6)	$F = 1.8$	0.164
Mean months of infection duration (SD)	179.7 (106.2)	278.6 (65.5)	166.8 (94.8)	$F = 20.6$	<0.001*
Mean recent CD4 count, cells/μL (SD)	590.7 (201.4)	411.8 (170.8)	934.3 (241.0)	$F = 54.9$	<0.001*
Mean nadir CD4 count, cells/μL (SD)	200 (288)	52 (123.2)	313 (272)	$H = 18.6$	<0.001*
Viral load undetectable (%)	100%	100%	100%	$\chi^2 = 0.0$	1.000
Substance use KMSK lifetime					
Med Alcohol score (IQR)	8 (8)	10 (3)	8 (8)	$H = 7.8$	0.020*
Med Tobacco score (IQR)	7 (10)	3.5 (11)	10 (12)	$H = 3.6$	0.164
Cocaine (% yes)	31.6%	60.6%	37.9%	$\chi^2 = 6.5$	0.039*
Opiates (% yes)	0%	8.8%	3.3%	$\chi^2 = 3.8$	0.148
Utox THC (% +)	48.7%	47.1%	50%	$\chi^2 = 0.6$	0.972
Utox Benzodiazepine (% +)	10.2%	11.8%	18.7%	$\chi^2 = 1.2$	0.548
Infection history					
Hepatitis B (% +)	17.9%	29.4%	15.6%	$\chi^2 = 2.2$	0.328
Tuberculosis (% +)	10.2%	8.8%	12.5%	$\chi^2 = 0.2$	0.887

Note.*Significant difference between groups $p < 0.05$; BDI-II = Beck Depression Inventory-II; KMSK = Kreek-McHugh-Schluger-Kellogg scale; Utox = Urine Toxicology Screen; THC = Tetrahydrocannabinol. Clusters differed by demographic variables. Cluster 2 and 3 included mainly participant with high ELS. However, cluster 2 included significantly older individuals, with more time of infection, lowest CD4 T-cell count, higher alcohol score than cluster 3.

Table 11.

Brain, Cognitive and Sex Risk Differences by Cluster Groups

	Cluster 1 (n=39)	Cluster 2 (n=34)	Cluster 3 (n=32)	*Test*	*p*
Education Quality					
Mean WRAT-3 (SD)	44.9 (9.5)	45.4 (9.4)	42.9 (9.1)	$F = 0.7$	0.518
Executive Function					
[a]Med CWIT (IQR)	64.0 (24.2)	62.3 (28.4)	66.0 (23.5)	$H = 1.4$	0.502
Mean Brain vols. cm^3 (SD)					
Orbitofrontal cortex	22526.2 (1665.5)	21487.2 (1260.8)	22060.6 (2091.1)	$F = 2.1$	0.125
Parietal lobe	103417.4 (9209.6)	102411.5 (7060.3)	101644.6 (9033.7)	$F = 0.7$	0.394
Insula cortex	12878.7 (972.8)	12403.5 (967.8)	12520.0 (1019.2)	$F = 1.8$	0.165
Caudate	6899.9 (758.6)	6849.5 (791.6)	6887.4 (823.5)	$F = 0.0$	0.980
Amygdala	3259.2 (326.0)	3235.8 (400.2)	3203.8 (322.9)	$F = 0.5$	0.579
Hippocampus	8062.4 (684.7)	8206.7 (918.7)	8018.9 (689.8)	$F = 0.2$	0.803
Anterior cingulate	4397.4 (534.5)	4399.5 (605.5)	4260.0 (706.7)	$F = 0.6$	0.570
Sex risk Behavior					
Condom use 6 mo. %				$\chi^2 = 11.2$	0.083
No sex/always	92%	82%	88%		
Most of time	0%	12%	0%		
Sometimes	5%	0%	6%		
Never	3%	6%	6%		
Condom lifetime %				$\chi^2 = 7.0$	0.324
No sex/always	21%	15%	9%		
Most of time	30%	41%	44%		
Sometimes	46%	44%	41%		
Never	3%	0%	6%		
Sex partners 6 mo. %				$\chi^2 = 10.0$	0.124
0	36%	50%	22%		
1	44%	23%	63%		
2 or 3	13%	23%	12%		
4	8%	3%	3%		
Sex partners lifetime %				$\chi^2 = 13.7$	0.033*
0 to 1	13%	0%	0%		
2 to 4	21%	15%	19%		
5 to 9	16%	12%	31.2%		
10 or more	50%	73%	50%		

Note.*Significant difference between groups $p < 0.05$, bolded *p* values when overall regression model survived FDR correction; [a]Lower scores are better; WRAT-3 = The Wide Range Achievement Test 3; CWIT= Color Word Test. No differerences were found in volumetric measures or sex risk behaviors.