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Neuroimaging and Cognitive Outcomes in Adults with Human Immunodeficiency Virus
and Early Life Stress

by

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Doctor of Philosophy in Psychology with an emphasis in Behavioral Neuroscience

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Abstract

Brain abnormalities persist in individuals with human immunodeficiency virus (HIV) despite the use of highly active antiretroviral therapy (HAART). To date, limited work has focused on the association between early life stress (ELS) and brain integrity in individuals with HIV, although ELS is highly prevalent in this population. The present study was conducted to determine whether ELS corresponds to the expression of persistent HIV-related neuroimaging abnormalities and cognitive dysfunction. A total of 130 HIV+ individuals on HAART and 76 HIV- individuals underwent 3T structural magnetic resonance imaging, diffusion tensor imaging, and neuropsychological assessment. Individuals were free of major psychiatric illness and neurological confounds. Participants were stratified into high or low ELS groups based on self-reported exposure to early life adversity using the Early Life Stress Questionnaire (ELSQ). No significant interactions were observed between HIV serostatus and ELS on white matter microstructural integrity, brain volumes, or cognition. However, HIV+ individuals exhibited significantly greater whole-brain white matter microstructural abnormalities, smaller brain volumes, and worse cognition compared to the HIV- group. Collapsed across HIV serostatus, individuals with high ELS demonstrated more severe whole-brain white matter microstructural abnormalities compared to individuals with low ELS. Results of present study suggest that high ELS is not a primary contributor to the neuropathogenic model of HIV in HAART-treated individuals. Evidence of persistent brain abnormalities among treated HIV+ individuals is consistent with results from other studies, further emphasizing the need to monitor cognitive health in patients after sustained HIV treatment.

Neuroimaging and cognitive outcomes in adults with human immunodeficiency virus and
early life stress

Human Immunodeficiency Virus (HIV) is a significant public health concern. The World Health Organization (WHO) estimates that over 35 million HIV+ individuals are currently living with the disease, with thousands of new cases diagnosed each year (WHO, 2017). Survival rates have improved dramatically since the introduction of highly active antiretroviral therapy (HAART) (Egger et al., 1997; Palella et al., 1998, 2006; Powderly, 2002). However, HIV penetrates the blood brain barrier within days of infection and is highly neurovirulent (Valcour et al., 2012), leading to inflammation and neuronal dysfunction. Despite the effectiveness of HAART in reducing viral load, increasing CD4 T-cell counts, and reducing opportunistic infections, current treatments do not prevent or reverse HIV-related brain damage (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Harezlak et al., 2011; Heaton et al., 2011).

Nearly half of all HIV+ patients exhibit some degree of neurocognitive impairment (Heaton et al., 2010; Heaton et al., 2011). There is a broad spectrum of cognitive variability in this population, with some individuals experiencing minimal or no cognitive dysfunction and others demonstrating dementia, the latter considered rare among individuals on suppressive antiretroviral treatment (Heaton et al., 2011; Robertson et al., 2007; Simioni et al., 2010). Consequently, understanding the role that co-morbid conditions play in the etiology of HIV-related neuroimaging abnormalities and cognitive dysfunction has become increasingly important. Nadir CD4 T-cell count, older age, and hepatitis C (HCV) co-infection contribute to cognitive variability in HIV (Becker, Lopez, Dew, & Aizenstein, 2004; Cherner et al., 2005; Devlin et al., 2012; Ellis et al., 2011;

Gongvatana et al., 2011; Hinkin, Castellon, Levine, Barclay, & Singer, 2008; Valcour et al., 2004, 2006).

Emerging evidence indicates that early life stress (ELS) may increase the risk of brain dysfunction in individuals with HIV (Clark et al., 2012; Clark, Sweet, Morgello, Philip, & Cohen, 2016; Spies et al., 2016). ELS is defined as one or more events during childhood that exceed a child's coping resources (Pechtel & Pizzagalli, 2011). Early life stressors include, but are not limited to, physical abuse, sexual abuse, emotional abuse, neglect, bullying, parental divorce, death of a family member, and sustained family conflict (De Bellis & Keshavan, 2003; Harrison, Fulkerson, & Beebem, 1997; McGee, Wolfe, Yuen, Wilson, & Carnochan, 1995; Sanders & Becker-Lausen, 1995). Notably, ELS is associated with an increased risk for depression and PTSD, as well as numerous medical conditions (e.g., cardiovascular disease, diabetes) in adulthood (Anda et al., 2002; Cicchetti, 2004; Dong et al., 2004; Edwards, Holden, Felitti, & Anda, 2003; Enoch, 2011; Nemeroff, 2016). Furthermore, a growing body of evidence indicates that ELS exerts pathological effects on the brain in otherwise healthy individuals (Andersen et al., 2008; Baker et al., 2013; Choi, Jeong, Rohan, Polcari, & Teicher, 2009; Cohen et al., 2006a; Gatt et al., 2009; Paul et al., 2008; Seckfort et al., 2008). Given that ELS is highly prevalent in HIV+ individuals (up to 76%; Simoni & Ng, 2000; Spies et al., 2012; Villar-Loubet et al., 2014; Walton et al., 2011) and detrimental to health, it is important to examine the relevance of ELS on brain integrity in HIV+ individuals.

ELS on Gray Matter and Cognitive Outcomes in HIV

Clark and colleagues (2012) conducted the first study to examine ELS on brain volumes and cognition in HIV+ individuals in comparison to HIV- controls. The Early

Life Stress Questionnaire (ELSQ; Sanders & Becker-Lausen, 1995) was administered to capture a range of ELS subtypes including interpersonal conflict, divorce, health, bullying, war, and natural disasters. HIV+ and HIV- individuals were classified as high ELS if they endorsed ≥ 3 events and low ELS if they reported < 3 events on the ELSQ. Results revealed significantly reduced psychomotor/processing and amygdala hypertrophy in HIV+ individuals with high ELS compared to HIV+ individuals with low ELS and HIV- controls. The finding of larger amygdala volume is unexpected as HIV+ adults typically exhibit lower brain volumes compared to HIV- controls (Ances et al., 2006, 2012; Behrman-Lay et al., 2016; Baker et al., 2015; Becker et al., 2012; Paul et al., 2016; Sanford et al., 2017).

More recently, Spies and colleagues (2016) examined the association between ELS and structural neuroimaging outcomes and cognitive performance in a sample of HIV+ females in South Africa. In this study, ELS was defined as a score of ≥ 41 on the Childhood Trauma Questionnaire- Short Form (CTQ-SF; Bernstein et al., 2003). Unlike the ELSQ, the CTQ-SF only examines childhood abuse and neglect. In this study, HIV+ females with ELS demonstrated smaller volumes of the anterior cingulate cortex, hippocampus, corpus callosum, caudate, and putamen compared with HIV+ females with no ELS and HIV- controls. Smaller brain volumes significantly correlated with worse performance on tests of motor skills, processing speed, learning, verbal fluency, attention/working memory, and abstraction/executive function (Supplemental Table 1). These results are consistent with the phenotype of HIV-related brain dysfunction (Ances et al., 2006, 2012; Behrman-Lay et al., 2016; Baker et al., 2014, 2015; Becker et al., 2012; Paul et al., 2014, 2016; Sanford et al., 2017; Spudich, 2013).

The two studies conducted to date suggest a deleterious correspondence between ELS and cognition, but inconsistent neuroimaging outcomes. Clark and colleagues (2012) revealed an isolated effect of ELS on amygdala hypertrophy in HIV+ individuals with high ELS, whereas Spies et al. (2016) demonstrated smaller volumes in numerous brain regions in HIV+ individuals with abuse and neglect compared with controls, in the absence of differences in amygdala volume. The conflicting results may reflect a number of cohort and methodological discrepancies between the studies, including depression status, self-report scales, select focus on abuse and neglect in the studies conducted by Spies et al. (2016), HIV treatment status, and viral load. The majority of participants enrolled by Clark et al. (2012) were on HAART (84%) and evidenced an undetectable viral load (74%). By contrast, less than 50% of the participants enrolled by Spies et al. (2016) were on HAART and, on average, exhibited a high viral load ($M = 116,172$ copies/ml). While it is possible that these differences may have contributed to the more robust neuroimaging outcomes observed in Spies et al. (2016), the specific explanation for the discrepancies between studies remains unknown.

ELS and White Matter in HIV

To date, studies have not examined the relationship between ELS and brain white matter. Specifically, white matter disruption (e.g., myelin pallor) is recognized as a neuroimaging abnormality related to HIV (Baker et al., 2017; Chen et al., 2009; Pomara, Crandall, Choi, Johnson, & Lim, 2001; Paul et al., 2016). ELS also related to pronounced neuroimaging abnormalities in brain white matter among HIV- individuals with and without psychopathology (e.g., Posttraumatic Stress Disorder [PTSD]; Anderson, 2008; Choi et al., 2009; Choi, Jeong, Polcari, Rohan, & Teicher, 2012; Paul et al., 2008;

Seckfort et al., 2008; Wang et al., 2010). Therefore, it is possible that ELS contributes to the etiology of white matter abnormalities that underlie some of the cognitive dysfunction in HIV. Investigating the association between ELS and white matter integrity in HIV+ individuals may help determine whether ELS-related mechanisms (e.g., HPA-axis dysfunction) represent new potential therapeutic targets for HIV-associated neurocognitive disorders.

Diffusion Tensor Imaging

Diffusion tensor imaging (DTI) measures the movement (diffusion) of water molecules in brain tissue. The imaging modality is particularly sensitive to alterations in white matter microstructure (Le Bihan et al., 2001). Damage to white matter pathways alters the speed and direction of diffusion along white matter fiber lengths and these changes can be quantified using DTI (Alexander, Lee, Lazar, & Field, 2007; Charlton et al., 2006; Song et al., 2002; Madden et al., 2012; Whitford, Kubicki, & Shenton, 2011). Common DTI indices include fractional anisotropy (FA), representing the ratio of directional to nondirectional diffusion, and mean diffusion (MD), representing unrestricted (isotropic) diffusion. Intact white matter is defined by highly anisotropic (directionally constrained) water diffusion (high FA, low MD), due to the underlying anatomy of the axon and the myelin sheath (Basser & Pierpaoli, 1996). Axial diffusivity (AD) and radial diffusivity (RD) characterize diffusion that occurs parallel (AD) and perpendicular (RD) to axons, likely representing axonal and myelin integrity, respectively (Alexander et al., 2007; Song et al., 2002).

Diffusion Tensor Imaging and Cognitive Studies of HIV

HIV is frequently associated with reduced FA, suggestive of reduced white matter integrity (Chen et al., 2009; Filippi, Ulu, Ryan, Ferrando, & van Gorp. 2001; Gongvatana et al., 2009; Hoare et al., 2012a; Leite et al., 2013; Pomara et al., 2001; Wang et al., 2015). Some studies also report increased MD, RD, and AD in chronically infected individuals, yet this pattern is not consistently observed. When present, DTI abnormalities associated with HIV are commonly observed in the frontal white matter and the corpus callosum (Cloak, Chang, & Ernst, 2004; Filippi et al., 2001; Heaps-Woodruff, Wright, Ances, Clifford, & Paul, 2016; Paul et al., 2016; Pomara et al., 2001; Thurnher et al., 2005; Wu et al., 2006). Research also indicates reduced white matter microstructural integrity in tracts that project to the frontal lobe, including the anterior thalamic radiation, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, cingulum bundle (cingulate gyrus and hippocampal segments of cingulum), and uncinate fasciculus (Gongvatana et al., 2009; Hoare et al., 2012b; Li et al., 2015; Paul et al., 2016; Pfefferbaum et al., 2009; Stubbe-Dräger et al., 2012; Tate et al., 2010; Wang et al., 2015; Wu et al., 2006; Zhu et al., 2013). DTI abnormalities in these tracts are associated with worse performance on tests of learning, memory, psychomotor/processing speed, gross motor, and executive function (Gongvatana et al., 2009; Hoare et al., 2012a&b; Stubbe - Dräger et al., 2012; Wu et al., 2006), emphasizing the functional significance of white matter disruption in the context of HIV.

Diffusion Tensor Imaging and Cognitive Studies of ELS

Numerous prior studies have suggested a significant association between ELS and white matter abnormalities in adults with and without psychopathology (e.g., depression, PTSD; Benedetti et al., 2014; Choi et al., 2009; Frodl et al., 2012; Huang, Gundapuneedi,

& Rao 2012; Lu et al., 2013; Paul et al., 2008; Seckfort et al., 2008). Importantly, there is significant overlap between the white matter neuroimaging signatures of HIV and ELS. For example, reduced white matter integrity in the corpus callosum is frequently observed in individuals with ELS (Benedetti et al., 2014; Huang et al., 2012; Lu et al., 2013; Paul et al., 2008; Seckfort et al., 2008). Research has also demonstrated significant relationships between ELS and white matter abnormalities in tracts traversing the frontal lobe such as the cingulum bundle, uncinate fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, and superior longitudinal fasciculus (Choi et al., 2009, 2012; Benedetti et al., 2014; Frodl et al., 2012; Huang et al., 2012). Collectively, these studies provide support that ELS may be associated with white matter integrity in adulthood.

The relationship between ELS and cognitive function is unclear. While one pilot study in healthy adults revealed that ELS may be associated with poorer memory performance (Majer, Nater, Lin, Capuron, & Reeves, 2010), most studies have focused on cognition and ELS in the context of overt psychopathology, including those with PTSD (Bremner, Vermetten, Afzal, & Vythilingam, 2004; Navalta, Polcari, Webster, Boghossian, & Teicher, 2006), schizophrenia (Aas et al., 2012; Lysaker, Myer, Evans, & Marks, 2001; Shannon et al., 2009), and major depressive disorder (MDD; Gould et al., 2012). However, it is important to note these relationships are not consistently observed in individuals with psychopathology (Stein, Koverola, Hanna, C, Torchia, & McClarty, 1997; Stein, Hanna, Vaerum, & Koverola, 1999) or in larger samples of otherwise healthy adults (Seckfort et al., 2008). Results from animal studies are more consistent. For example, rodents and non-human primates exhibit reduced learning and memory

following exposure to ELS (Aisa, Tordera, Lasheras, Del Río, & Ramírez, 2007; Avital, Ram, Maayan, Weizman, & Richter-Levin, 2006; Brunson et al., 2005; Meaney et al., 1991; Naninck et al., 2015; Sánchez, Hearn, Do, Rilling, & Herndon, 1998). These studies suggest that ELS may have direct links to cognitive ability, but research focused on ELS and cognition in humans has provided mixed support for this relationship. As such, the potential association between ELS and cognitive performance is unclear.

Summary

Two studies suggest a significant association between ELS and poorer cognitive outcomes in HIV+ individuals (Clark et al., 2012; Spies et al., 2016), however the relationship between co-morbid HIV and ELS on brain volumes remains unclear. Additionally, no study to date examined the relationship between HIV and ELS with white matter integrity. The present study addressed this important area by examining gray and white matter integrity, as well as cognition in 130 HIV+ and 76 HIV- individuals with high and low ELS exposure (assessed by the ELSQ). Participants underwent structural MRI, DTI, and neuropsychological assessment. All HIV+ participants were on HAART and all participants were free of major psychiatric illness and neurological confounds. It was hypothesized that HIV+ individuals with high ELS would exhibit abnormal DTI indices in the cingulum bundle, uncinate fasciculus, and corpus callosum and lower brain volumes in the anterior cingulate cortex, caudate, putamen, amygdala, hippocampus, and corpus callosum compared to HIV+ individuals with low ELS and HIV- controls. It was also predicted that reduced neuropsychological performance in the domains of executive function, psychomotor/processing speed, and learning would be observed in HIV+ individuals with high ELS compared to the two HIV- control groups.

The objective of this study was to develop a more comprehensive understanding of the relationship between high ELS with neuroimaging outcomes and cognitive function in HIV+ individuals.

Study Overview

The study was funded by the National Institutes of Health (F31-MH105308; PI: Ms. Laurie Baker; Mentors: Drs. Robert Paul, Beau Ances, and Michael Griffin). The data were extracted from three larger studies focused on brain integrity in adults with HIV (R01-NR012657; R01-NR012907; R01-NR014449; PI: Dr. Beau Ances). The parent grants did not focus on ELS, and therefore the current study reflected a unique element of research that leveraged the strengths of existing studies.

Research Design Considerations

A number of important methodological design issues were considered to ensure high scientific rigor. The initial design consideration was whether the retrospective, self-report measure of ELS (ELSQ) was an adequate assessment of ELS. Retrospective reports of ELS are often subject to recall bias (Hardt & Rutter 2004), therefore prospective studies of ELS on the brain are preferable. However, this approach was not feasible in this particular cohort given that individuals were evaluated in adulthood. Fortunately, numerous studies reveal that the ELSQ is sensitive to alterations in brain integrity related to ELS (Baker et al., 2013; Cohen et al., 2006a; Gatt et al., 2009; Paul et al., 2008; Seckfort et al., 2008) and co-morbid HIV and ELS (Clark et al., 2012; Clark et al., 2016). Furthermore, this measure has strong internal consistency ($\alpha = 0.90$) and test-retest reliability ($r = 0.89$; $p < 0.001$).

The second consideration was the method to classify ELS groups. Numerous

previous studies utilized a cut point of ≥ 2 (Cohen et al., 2006a; Hoth et al., 2006) or ≥ 3 ELS events (Clark et al., 2012, 2016; Korgaonkar et al., 2013; McFarlane et al., 2005; Paul et al., 2008; Seckfort et al., 2008) on the ELSQ to define high ELS. In the present study, ≥ 3 ELS events was chosen as the threshold for high ELS to allow for direct comparison with the most relevant extant literature in co-morbid HIV and ELS (Clark et al., 2012). Additionally, previous studies using the ELSQ defined low or no ELS by < 3 (Clark et al., 2012; Korgaonkar et al., 2013; Seckfort et al., 2008) or 0 ELS events (Cohen et al., 2006a; McFarlane et al., 2005; Paul et al., 2008). A cut-point of < 3 allows for maximum data inclusion in the present study and is consistent with recent literature in co-morbid HIV and ELS (Clark et al., 2012; Clark et al., 2016). As such, the final classification rules for primary analyses were: 1) high ELS defined by ≥ 3 ELS events, 2) low ELS defined by < 3 ELS events.

One limitation of the selected method is that a cut-point of < 3 to define low ELS does not provide a large distinction between high and low ELS groups. Therefore, exploratory analyses were used to determine whether differences in brain integrity were present between individuals with high ELS defined by ≥ 3 ELS events and low ELS defined by < 2 ELS events. While 0 ELS events would allow for maximum distinction between groups, only 11% of HIV+ participants reported no ELS, consistent with rates observed in prior HIV studies (Clark et al., 2012, 2016; Mugavero et al., 2006), while 24% reported < 2 ELS events. Additionally, studies have demonstrated a dose-response curve between ELS events and brain abnormalities (Cohen et al., 2006a; Paul et al., 2008), therefore the number of ELS events was examined as a continuous variable in exploratory analyses. Lastly, childhood abuse and neglect are frequently associated with

neuroimaging abnormalities (Anderson et al., 2008; Chaney et al., 2014; Stein et al., 1997), therefore exploratory analyses examined whether individuals that experienced abuse and/or neglect exhibited worse brain outcomes than those that experienced other forms of ELS.

The third consideration was the selection of white matter tracts. The corpus callosum is a dense white matter tract containing interhemispheric cortical connections and abnormalities in this region are frequently associated with cognitive dysfunction (Hoare et al., 2012a&b; Sullivan, Adalsteinsson, & Pfefferbaum, 2006; Wu et al., 2006). Studies have reported white matter abnormalities in the corpus callosum in HIV+ individuals (Filippi et al., 2001; Heaps-Woodruff et al., 2016; Tate et al., 2010; Wright, Heaps, Shimony, Thomas, & Ances, 2012; Wu et al., 2006) and in adults with ELS (Benedetti et al., 2014; Frodl et al., 2012; Huang et al., 2012; Lu et al., 2013; Paul et al., 2008; Poletti et al., 2015; Seckfort et al., 2008). As such, the corpus callosum is an ideal target to investigate co-morbid HIV and ELS on white matter integrity. The uncinate fasciculus and cingulum bundle connect prefrontal, medial temporal, and the cingulate cortices and are associated with aspects of executive functioning, psychomotor/processing speed, and learning, as well as emotional processing (Etkin, Egner, & Kalisch, 2011; Schulte, Müller-Oehring, Sullivan, & Pfefferbaum, 2012; Davis et al., 2009; Diao et al., 2015; Johnson et al., 2011; Sasson, Doniger, Pasternak, Tarrasch, & Assaf, 2013). Further, these tracts are independently associated with HIV (Fillippi et al., 2001; Heaps-Woodruff et al., 2016, Wright et al., 2012; Paul et al., 2016; Wu et al., 2006) and ELS (Choi et al., 2009; Huang et al., 2012; Lu et al., 2013; Paul et al., 2008; Poletti et al., 2015; Seckfort et al., 2008). Therefore, the present study focused on the

corpus callosum, uncinate fasciculus, and cingulum bundle as primary white matter tracts of interest. Several studies have also demonstrated widespread white matter injury in HIV+ individuals (Baker et al., 2017; Chen et al., 2009; Nir et al., 2014; Ragin, Storey, Cohen, Edelman, & Epstein, 2004; Ragin, Storey, Cohen, Epstein, & Edelman, 2004; Stubbe-Dräger et al., 2012; Su et al., 2016; Underwood et al., 2017). As such, whole-brain white matter integrity at the voxel level was examined as an exploratory aim.

Method

Participants

Data from 130 HIV+ individuals with an average age of 51.0 years ($SD = 13.2$) and 13.0 years of education ($SD = 2.7$), and 76 HIV– individuals with an average age of 35.6 years ($SD = 16.0$) and 13.8 years of education ($SD = 2.0$) were extracted from archival databases. Participants were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic in Saint Louis, the WUSM AIDS Clinical Trial Group (ACTG) community medical providers, and local organizations. A similar recruitment strategy was employed for all participants in attempt to match the HIV+ and HIV– groups on demographic and historical factors that could negatively impact brain integrity. Participation was voluntary and individuals were informed they could withdraw from the study at any time. Written informed consent was obtained following a thorough explanation of the study procedures. Cognitive data, ELS quantification, participant demographics and relevant health histories were obtained at WUSM. Neuroimaging procedures were completed in all individuals at WUSM within one week of the neuropsychological visit. The Institutional Review Board of the University of Missouri-St. Louis and WUSM approved the study protocol as part of the parent grants and the

NIH F31 award. All participants received financial compensation for their involvement in the study.

Inclusion/Exclusion Criteria

Individuals were included in the study if they met the following criteria: 1) at least 18 years of age; 2) at least 8 years of formal education; and 3) initiation of HAART at least three months prior to enrollment for HIV+ individuals. HIV- controls were administered a rapid oral HIV buccal test to confirm a negative result at the time of enrollment. Participants were excluded if they met any of the following criteria: 1) unable to provide written consent determined by the failure to answer questions outlined in the informed consent about study procedures, risks, and, benefits of study; 2) any neurological disorders associated with neurocognitive impairment other than HIV (e.g., multiple sclerosis); 3) active opportunistic infection (e.g., cytomegalovirus encephalitis, cryptococcal meningitis, toxoplasma encephalitis); 4) HCV co-infection; 5) lifetime history of head injury with a loss of consciousness > 30 minutes; 6) major psychiatric illness (e.g., schizophrenia, bipolar disorder), PTSD, or current severe depression (determined by a score ≥ 29 on the Beck Depression Inventory-II; BDI-II; Beck, Steer, & Brown, 1996); 7) pregnancy determined by a urine pregnancy test prior to testing; and 8) contraindications for MRI (e.g., claustrophobia, metal exposure).

Disease Characteristics

HIV serostatus was determined using an HIV antibody test and confirmed by Western blot. A blood sample was obtained from all HIV+ participants to measure CD4 T-cell counts and plasma HIV viral load within 30 days prior to neuropsychological assessment and neuroimaging acquisition. Nadir CD4 T-cell count, duration of infection,

duration of HAART, estimated gap between HIV diagnosis and initiation of HAART, and type of HAART regimen were obtained from self-report or medical records, when available.

Early Life Stress Questionnaire (ELSQ)

The ELSQ is based on the Child Abuse and Trauma Scale (Sanders & Becker-Lausen, 1995). The ELSQ consists of 19 items that ask whether or not the individual experienced ELS events such as physical abuse, emotional abuse, sexual abuse, bullying, neglect, poverty, parental divorce, and domestic violence. The participants were asked to respond “yes” or “no” to each event and identify the age of onset (0–17 years of age). The high ELS group was defined by the endorsement of ≥ 3 ELS events. The low ELS group was defined by the endorsement of < 3 ELS events. Individuals were divided into four groups for primary analyses (HIV+/high ELS $n = 91$; HIV+/low ELS $n = 39$; HIV–/high ELS $n = 45$; HIV–/low ELS $n = 31$). For exploratory analyses, the high ELS group was defined by the endorsement of ≥ 3 ELS events and the low ELS group was defined by the endorsement of < 2 ELS events (HIV+/high ELS $n = 91$; HIV+/low ELS $n = 23$; HIV–/high ELS $n = 45$; HIV–/low ELS $n = 27$). For additional exploratory analyses, HIV+ individuals were separated into two groups based on whether or not they experienced abuse and/or neglect by the endorsement of one or more of the following questions on the ELSQ: 1) Were you physically abused? 2) Were you sexually abused? 3) Were you emotionally abused? 4) Did you experience extreme poverty or neglect?

Beck Depression Inventory II (BDI-II)

The BDI-II (Beck et al., 1996) is a 21-item self-report instrument intended to assess the existence and severity depression symptoms as listed in the Diagnostic and

Statistical Manual of Mental Disorders Fourth Edition (DSM-IV; American Psychiatric Association, 1994). A total score of 0–13 is considered minimal depression, 14–19 is mild, 20–28 is moderate, and 29–63 is severe. Participants with a BDI-II total score ≥ 29 were excluded.

Neuroimaging

Neuroimaging Acquisition

All neuroimaging was obtained at WUSM on a 3T Siemens Tim Trio whole body MR scanner at (Siemens AG, Erlangen Germany) using a 12-channel transmit/receive head coil. A T1-weighted three-dimensional magnetization-prepared 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 mm³) was obtained. Two acquisitions of diffusion-weighted images were collected and subsequently averaged for the assessment of white matter microstructural integrity (2 x 2 x 2 mm³ voxels, TR= 9900 ms, TE = 102 ms, flip angle =90°, 23 directions with multiple b values ranging between 0 and 1400 s/mm²).

Diffusion Tensor Imaging Processing

DTI preprocessing included correction for eddy current distortions followed by skull stripping (Smith, 2002) using FSL 5.0.9 (www.fmrib.ox.ac.uk/fsl/). Scans confounded by head movement > 3 mm were discarded (Strain et al., 2017). Tensor calculation for FA, MD, AD, and RD were derived using the Functional Magnetic Resonance Imaging of the Brain (FMRIB) software library (FSL) for preparation of tract based spatial statistics (TBSS; Smith et al., 2006).

A voxel-wise analysis was performed using the TBSS package, part of FSL

(Smith et al., 2006). FA maps were aligned to the FA standard image using the FMRIB nonlinear image registration tool (Jenkinson & Smith, 2001; Jenkinson, Bannister, Brady, & Smith, 2002). A group specific mean FA map was created and thinned to produce a mean skeleton. A threshold of $FA = 0.25$ was used as it provides confidence that the voxels selected are primarily white matter voxels rather than voxels consisting of partial gray/partial white matter. Contrast analyses of the entire white matter skeleton for each diffusion metric were performed using the “Randomise” tool in FSL (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). A Monte Carlo permutation based approach was used to correct for multiple comparisons (Smith & Nichols, 2009).

In addition to the voxel-wise analysis of the skeletonized data, tract-wise analyses were conducted by isolating the portions of the TBSS-derived skeleton that fell within the boundaries of a priori white matter tract regions. The cingulum bundle (cingulate gyrus segment of cingulum and hippocampal segment of cingulum) and uncinate fasciculus were modeled separately by hemisphere and streamlines were selected for inclusion using the JHU atlas (Mori, Wakana, Nagae-Poetscher, & Van Zijl, 2005). Additionally, a mask of the whole corpus callosum was manually traced on the midsagittal slice of the T2-weighted image. The adjacent slices were checked to ensure that the midsagittal slice contained the full corpus callosum.

Volumetric Analysis

Quantification of regional volumes was obtained using the FreeSurfer software suite (v5.1) (Martinos Center, Harvard University, Boston, MA; <http://surfer.nmr.mgh.harvard.edu>). This automated software program transforms the MPRAGE scan of an individual into a template space with the skull stripped and the

brain segmented into white matter, gray matter, and ventricles. Brain regions were parcellated into subcortical and cortical regions of interest (ROI) using a surface deformation program (Dale, Fischl, & Sereno, 1999; Fischl et al., 1999; Desikan et al., 2006). Images from all subjects were aligned onto a common atlas (MNI305) (Fischl et al. 2004). For this analysis, strategic ROIs included: anterior cingulate cortex, caudate, putamen, amygdala, hippocampus, and corpus callosum. All volumetric analyses included total intracranial volume (ICV) as a covariate to control for individual differences in head size.

Neuropsychological Assessment

All participants completed a comprehensive neuropsychological evaluation at WUSM. The neuropsychological tests were chosen based on established sensitivity to HIV-associated cognitive dysfunction (Baker et al., 2014, 2015; Grant, 2008; Robertson et al., 2007). Raw scores from each cognitive test were included in analyses. For descriptive purposes, raw scores were converted to standardized z-scores using published normative standards with adjustments for demographics where applicable (Supplemental Table 2; Benedict, Schretlen, Groninger, & Brandt, 1998, Delis, Kaplan, & Kramer, 2001; Friedman, Schinka, Mortimer, & Graves, 2002; Heaton, Miller, Taylor, & Grant, 2004.; Lucas et al., 2005; Norman et al., 2011; Piatt, Fields, Paolo, & Tröster, 2004; Wechsler, 1997; Woods et al., 2005b). Individual test z-scores were averaged by domain to create domain-specific z scores (psychomotor/processing speed, executive function, learning). Participants were classified as cognitively impaired if they had a z score of < -1.0 in two or more cognitive domains or a z score of < -2.0 in at least one cognitive domain. Classified in this manner, 33% of HIV+ individuals demonstrated cognitive

impairment, generally consistent with numerous studies in the HAART-era (Heaton et al., 2010; McCutchan et al., 2007; Sacktor et al., 2016; Robertson et al., 2007), compared with 24% in the HIV– group. Rates of cognitive impairment in each group (HIV+/high ELS; HIV+/low ELS; HIV–/high ELS; HIV–/low ELS) are reported in Table 1.

Psychomotor/Processing Speed

The following tests measured psychomotor/processing speed: 1) Trails A from the Trail Making Test (Reitan & Davison, 1974), 2) Grooved Pegboard-dominant and non-dominant hand (Kløve, 1963), and 3) Digit Symbol from the Wechsler Adult Intelligence Scale-III (WAIS-III; Wechsler, 1997). Trails A requires participants to connect a series of numbers in numerical order such that a line is drawn from 1 to 2 to 3, etc. Time to completion in seconds was the primary outcome measure. During the Grooved Pegboard test, participants are asked to insert grooved metal pegs into holes aligned in different rotations. The pegs must be rotated to match the hole before they can be inserted. Participants start with their dominant hand and place the pegs into the holes as fast as they can without skipping any, then must complete the same task with their non-dominant hand. Time to completion was the primary outcome measure for both dominant and non-dominant hands. The Digit Symbol task requires participants to match symbols to their corresponding digit. The primary outcome measure was total correct in 120 seconds.

Executive Function

The following tests were used to measure executive function: 1) Trails B from the Trail Making Test (Reitan & Davison, 1974), 2) Verb Fluency (Piatt, Fields, Paolo, & Tröster, 1999), 3) Letter Number Sequencing (LNS) from the WAIS-III (Wechsler, 1997), and 4) Trial 3 of the Color Word Interference Task (CWIT; Delis, Kaplan, &

Kramer, 2001). Trails B requires participants to connect numbers in ascending order and letters in alphabetical order in an alternating sequence. Numbers and letters are connected by drawing a line from 1 to A, A to 2, 2 to B, etc. Time to completion was the primary outcome measure. Verb fluency requires participants to recite as many verbs as they can in 60 seconds. The number of correctly stated verbs on the entire test was the primary outcome measure. LNS requires participants to arrange a series of numbers and letters within a string by placing numbers in order first, followed by letters in alphabetical order. Each letter-number string has a distinct amount of characters (begins with 2 and ends at 9) and there are three strings within a block. The task is concluded once a participant fails to complete all three strings within a block. The number of successfully completed strings was the primary outcome measure. During Trial 3 of the CWIT, participants are presented with four rows of color-words (e.g. the word red) that are printed in a contrasting color-word combination (e.g. the word red printed in blue ink). Participants are required to identify the ink color of each color-word. Time to completion was the primary outcome measure.

Learning

The Hopkins Verbal Learning Test-Revised (HVLTR; Brandt & Benedict, 2001) was administered to measure learning. The HVLTR consists of a 12-item word list, composed of four words from three semantic categories (e.g. precious stones, human shelter, animals). Participants are asked to recall the words, in any order, after the list had been read to them. The primary outcome measure was the total number of recalled words over three trials. Immediate recall is most commonly impacted by HIV, therefore the

retention and recognition subtests of the HVLT-R were not included in analyses (Cohen, Seider, & Navia, 2015; Grant, 2008; Woods, Moore, Weber, & Grant, 2009).

Statistical Analyses

Data Cleaning:

Data was screened for outliers ($z \geq \pm 3$ standard deviations from the group mean) and missing values. The number of missing cases represented less than 10% in each group, therefore mean imputation was employed to address missing data (Peng, Harwell, Liou, & Ehman, 2006; Pineau, Marchand, & Guay, 2014; Tabachnick & Fidell, 2007). Data were screened for normality using Q-Q plots. Results of these analyses concluded that DTI, brain volume, and neuropsychological data did not violate assumptions of normality.

Factorial univariate analyses of variance/univariate analyses of covariance (ANOVA/ANCOVA) or multivariate analyses of variance/multivariate analyses of covariance (MANOVA/MANCOVA) models were used for all primary analyses. Each dependent variable was checked for normality, linearity, multivariate outliers, homogenous covariance matrices, and multicollinearity to ensure all variables met necessary assumptions for using these statistical tests. Variables that were non-normally distributed were log transformed and re-examined for normality. Pillai's Trace was used to report results for MANOVAs that violated statistical assumptions of homogeneity of variance (Box's $M < 0.001$, Bartlett's test > 0.001 , Levene's test < 0.05 ; Meyers, Gamst, & Guarino, 2006). Assumptions were met unless otherwise noted in the results. Statistical significance was determined using an alpha level of 0.05. False discovery rate (FDR;

Benjamini & Hochberg, 1995) corrections were implemented for all family-wise analyses to control Type 1 error rate.

Examination of demographic, disease, and psychiatric variables:

Preliminary analyses examined demographic, disease, and psychiatric variables between the four groups for primary analyses (HIV+/high ELS, HIV+/low ELS, HIV–/high ELS, HIV–/low ELS). Separate ANOVAs were used to determine if the groups differed in age, years of education, and/or BDI-II across the four groups. Chi-square analyses determined potential differences in sex, race, and self-reported drug and alcohol use (≥ 1 instance of self-reported use in last 6 months) between the four groups. Separate independent samples *t*-tests were conducted to detect potential differences in current CD4 T-cell count, nadir CD4 T-cell count, current viral load (\log_{10} transformed), duration of infection, duration of HAART, and estimated gap between HIV diagnosis and initiation of HAART between the HIV+/high ELS group and HIV+/low ELS group. Potential differences in the number of detectable (> 20 RNA copies/ml) versus undetectable viral load (≤ 20 RNA copies/ml) and types of HAART regimens were examined using chi-squared analyses. Demographic, disease, and psychiatric variables that differed significantly ($p < 0.05$) between groups and were at least moderately correlated ($r \geq 0.30$ with one or more of the dependent variables) were included as covariates in the main analyses to control for intervening effects on the outcome measures (Tavakoli, 2012).

Differences in demographic, disease, and psychiatric variables were also examined between groups. For Exploratory Aim 3, independent samples *t*-tests for continuous variables (e.g., age, education) and chi-square analyses for categorical variables (e.g., sex, race) were used to determine differences between HIV+ individuals

that experienced abuse and/or neglect and those that did not. For Exploratory Aim 4, the same variables were analyzed between the four groups with high ELS defined by ≥ 3 ELS events and low ELS defined by < 2 ELS events (HIV+/high ELS $n = 92$; HIV+/low ELS $n = 23$; HIV-/high ELS $n = 45$; HIV-/low ELS $n = 27$) using separate ANOVAs for continuous variables and chi-square analyses for categorical variables. Demographic, disease, and psychiatric variables that differed significantly ($p < 0.05$) between groups and were at least moderately correlated ($r \geq 0.30$ with one or more of the dependent variables) were included as covariates in the respective exploratory analyses.

Data Reduction:

Correlation analyses between DTI metrics revealed strong associations (r 's > 0.70) between MD and RD for nearly all tracts. Therefore, MD was eliminated from analyses to reduce redundancy. Correlations between FA, RD, and AD were < 0.70 across each of the tracts, therefore all three metrics were used in analyses. Bivariate correlations revealed moderate to large correlations between all imaging indices obtained in the left and right hemispheres (r 's = 0.50-0.80). As such, the tracts were aggregated into single bilateral tracts, consistent with prior work (e.g., Filippi et al., 2001; Pomara et al., 2001; Thurnher et al., 2005; Wu et al., 2006).

Primary Aims

Analytic Plan for Aim 1: Determine the association between ELS and white matter integrity in HIV+ and HIV- individuals. H₁: HIV+ individuals with high ELS will exhibit significantly lower FA and higher AD and RD in the corpus callosum, uncinate fasciculus, and cingulum bundle compared to HIV+ individuals with low ELS and HIV- individuals with high and low ELS. Three separate 2x2

factorial MANCOVAs with factors of HIV status (HIV+, HIV-) and ELS status (low ELS, high ELS) were used to compare FA, AD, and RD values between the four groups and to examine the interaction between HIV and ELS status. Age and sex were controlled in each MANCOVA (Table 1). HIV and ELS status served as the independent variables in each analysis and FA, AD, and RD values served as the dependent variables. If a significant HIV x ELS interaction was observed, follow-up analyses of the simple main effects (mean differences between the HIV+/high ELS, HIV+/low ELS, HIV-/high ELS, and HIV-/low ELS groups) were conducted. If the interaction analysis did not demonstrate statistical significance, the main effects (HIV status and ELS status) were then examined for significance. In the presence of significant main effects for HIV and/or ELS, univariate analyses were used to determine which white matter tract diffusion values differed significantly between groups. Group means were examined to determine the direction of any significant main effects.

Analytic Plan for Aim 2: Determine the association between ELS and gray matter volumes in HIV+ and HIV- individuals. H₂: HIV+ individuals with high ELS will exhibit smaller volumes in the anterior cingulate cortex, hippocampus, putamen, amygdala, corpus callosum and caudate compared to HIV+ individuals with low ELS and HIV- individuals with and high and low ELS. A 2x2 factorial MANCOVA with factors of HIV status (HIV+, HIV-) and ELS status (low ELS, high ELS) was used to compare brain volumes between the four groups and to examine the interaction between HIV and ELS status. Age, sex, and ICV were controlled in the MANCOVA (Table 1). HIV and ELS status served as the independent variables in each

analysis and brain volumes served as the dependent variables. Follow-up analyses were conducted, if necessary, as described in Primary Aim 1.

Analytic Plan for Aim 3: Determine the association between ELS and neuropsychological performance in HIV+ and HIV– individuals. H₃: HIV+ individuals with high ELS will perform more poorly on tests of psychomotor/processing speed, executive function, and learning compared to HIV– individuals with high and low ELS. Raw scores on psychomotor/processing speed, executive function, and learning tests were analyzed in three separate 2x2 factorial MANCOVAs (or ANCOVA, when appropriate) (one for each domain). Factors of HIV status (HIV+, HIV–) and ELS status (low ELS, high ELS) were used to compare performance between the four groups and to examine the interaction between HIV and ELS status. HIV and ELS status served as the independent variables in each analysis and raw scores on each cognitive test served as the dependent variables. Each analysis controlled for age and sex (Table 1). Follow-up analyses were conducted, if necessary, as described in Primary Aim 1. **H₄: Alterations in white matter tract integrity and brain volumes will predict cognitive performance in HIV+ individuals with high ELS.** Bivariate correlations were utilized to determine whether the cognitive tests that significantly differed between groups in Primary Aim 3 were associated with white matter tracts and brain volumes that significantly differed between groups in Primary Aims 1 and 2.

Exploratory Aims

Exploratory Aim 1: Examine the relationship between ELS and whole-brain white matter integrity using voxel-wise analyses in HIV+ and HIV– individuals.

Analyses of the entire white matter skeleton for each diffusion metric were performed using the “Randomise” tool in FSL. F-tests with factors of HIV status (HIV+, HIV-) and ELS status (low ELS, high ELS) were used to examine the interaction between HIV status and ELS status on whole-brain FA, AD, and RD. HIV and ELS status served as the independent variables in each analysis and whole-brain FA, AD, and RD values served as the dependent variables. Follow-up analyses were conducted, if necessary, as described in Primary Aim 1. Each analysis controlled for age and sex at the voxel level and correction for multiple comparisons was conducted using a Monte Carlo 5000 permutation based approach (Smith & Nichols, 2009).

Exploratory Aim 2: Investigate the cumulative effect of ELS on white matter integrity, brain volumes, and cognitive performance in HIV+ individuals. Linear regression analyses were utilized to examine the relationship between the total number of ELS events and DTI metrics, brain volumes, and neuropsychological performance. The first component was addressed through regression models including the number of ELS events as the independent variable and FA, AD, and RD values of the white matter tracts of interest as the dependent variables (one linear regression for each DTI metric). The second component was addressed through regression models including the number of ELS events as the independent variable and brain volumes as the dependent variables, controlling for ICV. The third component was addressed through regression models including the number of ELS events as the independent variable and raw scores within each neuropsychological domain (one linear regression for each domain for psychomotor/processing speed and executive function) as the dependent variables. A bivariate correlation was used to examine the relationship between number of ELS events

and learning.

Exploratory Aim 3: Determine differences in neuroimaging outcomes and neuropsychological performance in HIV+ individuals who experienced abuse and/or neglect and those that did not. The HIV+ group was separated into two groups based on whether or not they endorsed one or more abuse and/or neglect items on the ELSQ, regardless of high or low ELS grouping in the primary analyses. Separate ANOVAS or MANOVAS (ANCOVAs or MANCOVAs, where appropriate) were used to examine differences in DTI metrics, volumes, and cognition between groups with history of abuse/neglect and those without. The abuse/neglect groups described above served as the independent variable and diffusion metrics (one model for each diffusion metric), brain volumes, and cognitive test performance (one model for each domain) served as the dependent variables. The analysis examining differences in brain volumes controlled for ICV.

Exploratory Aim 4: Determine the association between ELS and white matter integrity, brain volumes, and neuropsychological performance in HIV+ and HIV– individuals with high ELS defined by ≥ 3 ELS events and low ELS defined by < 2 ELS events. Separate 2x2 factorial MANCOVAs (or ANCOVAs, when appropriate) with factors of HIV status (HIV+, HIV–) and ELS status (low ELS; < 2 ELS events, high ELS; ≥ 3 ELS events) were used to compare diffusion metrics, brain volumes, and cognitive test performance between the four groups and to examine the interaction between HIV and ELS status. The same statistical procedures as described in Primary Aims 1-3 were implemented for each MANCOVA (or ANCOVA). Age and sex were

controlled in each MANCOVA (or ANCOVA, when appropriate). ICV was also included as a covariate in the analysis examining brain volumes.

Results

Data Screening and Preliminary Analyses

The final sample was comprised of 206 participants. Overall, the entire sample included 140 males (68%) and 66 females (32%). The majority of participants were African American (57%), followed by Caucasian (40%), multi-racial (2%), and Asian (1%). The average age collapsed across groups was 45.5 years ($SD = 16.01$; range = 18-80) and the average education level was 13.6 years ($SD = 2.5$; range = 8-20).

Comparisons by HIV/ELS groups indicated that the groups significantly differed in age ($F(3, 202) = 20.31, p = 0.02, \eta_p^2 = 0.23$), sex ($\chi^2(3, n = 206) = 23.67, p < 0.01, Cramer's V = 0.33$) and BDI-II score ($F(3, 201) = 3.48, p < 0.01, \eta_p^2 = 0.05$). Age was significantly related to a majority of the dependent variables in each primary analysis ($r's > 0.30, p's < 0.05$). Additionally, independent samples t -tests revealed significant differences between males and females in numerous dependent variables for each primary aim ($p's < 0.05$). As such, both variables were included as covariates in the primary analyses. BDI-II scores were significantly different between HIV/ELS groups, however scores were not moderately correlated with any DTI metrics, brain volumes, or individual neuropsychological test scores ($r < 0.30$). Therefore, BDI-II score was not included as a covariate in primary analyses. No group differences were observed for years of education ($F(3, 202) = 1.14, p = 0.33, \eta_p^2 = 0.02$) or race ($\chi^2(12, n = 206) = 15.47, p = 0.22, V = 0.16$). Further, no significant differences were present between the four groups self-reported use in the last 6 months of opioids ($\chi^2(3, n = 185) = 2.43, p =$

0.49, $V = 0.12$), amphetamines ($\chi^2(3, n = 184) = 4.62, p = 0.20, V = 0.20$), crack/cocaine ($\chi^2(3, n = 187) = 3.12, p = 0.37, V = 0.37$), marijuana ($\chi^2(3, n = 198) = 1.28, p = 0.73, V = 0.08$), or alcohol ($\chi^2(3, n = 196) = 1.04, p = 0.79, V = 0.07$).

There were no significant differences in disease factors including duration of infection ($t(128) = 1.29, p = 0.20, d = 0.25$), current viral load ($t(121) = -0.11, p = 0.28, d = 0.01$), number of individuals with detectable versus undetectable viral load ($\chi^2(1, n = 123) = 0.21, p = 0.64, V = 0.04$), current CD4 T-cell count ($t(120) = 0.78, p = 0.39, d = 0.15$), nadir CD4- T- cell count ($t(109) = -0.13, p = 0.87, d = 0.02$), duration of HAART ($t(127) = 0.93, p = 0.35, d = 0.21$), estimated gap between HIV diagnosis and initiation of HAART ($t(122) = 1.16, p = 0.25, d = 0.18$), and type of HAART regimen ($\chi^2(3, n = 129) = 2.95, p = 0.40, V = 0.15$). All HIV+ participants were on HAART. Sample characteristics are listed in Table 1.

No significant differences between demographic, disease, and psychiatric variables were observed between HIV+ individuals that experienced abuse and/or neglect and those experienced other types of ELS (p 's > 0.05), therefore no covariates were used in Exploratory Aim 3. However, comparisons by HIV/ELS groups (high ELS defined by ≥ 3 ELS events and low ELS defined by < 2 ELS events) indicated that the groups significantly differed in age ($F(3, 182) = 18.09, p < 0.01, \eta_p^2 = 0.23$), sex ($\chi^2(3, n = 186) = 25.27, p < 0.01, V = 0.34$), and BDI-II score ($F(3, 186) = 3.78, p = 0.01, \eta_p^2 = 0.06$). Age was significantly related to a majority of the dependent variables in each primary analysis (r 's $> 0.30, p$'s < 0.05). Additionally, independent samples t -tests revealed significant differences between males and females in numerous dependent variables for each primary aim (p 's < 0.05). As such, both variables were included as covariates in the

primary analyses. BDI-II scores were significantly different between HIV/ELS groups, however scores were not moderately correlated with any DTI metrics, brain volumes, or individual neuropsychological test scores ($r < 0.30$). Therefore, BDI-II score was not included as a covariate in Exploratory Aim 4. No other significant differences in demographic, psychiatric, or disease characteristics were observed between the four groups (p 's > 0.05).

Primary Aims

No HIV x ELS interaction was observed for FA (Wilks' $\Lambda = 0.99$, $F(4, 195) = 0.12$, $p = 0.98$, $\eta_p^2 < 0.01$), AD (Wilks' $\Lambda = 0.99$, $F(4, 192) = 0.50$, $p = 0.74$, $\eta_p^2 = 0.01$), or RD (Pillai's Trace = 0.01, $F(4, 193) = 0.24$, $p = 0.91$, $\eta_p^2 < 0.01$). Additionally, no main effects of HIV were observed on FA (Wilks' $\Lambda = 0.98$, $F(12, 195) = 0.57$, $p = 0.97$, $\eta_p^2 < 0.01$), AD (Wilks' $\Lambda = 0.97$, $F(4, 192) = 1.66$, $p = 0.16$, $\eta_p^2 = 0.03$), or RD (Pillai's Trace = 0.01, $F(4, 193) = 0.37$, $p = 0.83$, $\eta_p^2 < 0.01$). There were also no main effects of ELS on FA (Wilks' $\Lambda = 0.99$, $F(4, 195) = 0.39$, $p = 0.69$, $\eta_p^2 = 0.01$), AD (Wilks' $\Lambda = 0.97$, $F(4, 192) = 1.66$, $p = 0.66$, $\eta_p^2 = 0.01$), or RD (Pillai's Trace = 0.01, $F(4, 193) = 0.29$, $p = 0.88$, $\eta_p^2 < 0.01$; Table 2).

Similarly, no HIV x ELS interaction was observed on brain volumes (Wilks' $\Lambda = 0.98$, $F(6, 187) = 0.70$, $p = 0.65$, $\eta_p^2 = 0.02$). However, there was a significant main effect of HIV on brain volumes (Wilks' $\Lambda = 0.91=9$, $F(6, 187) = 3.51$, $p < 0.01$, $\eta_p^2 = 0.10$). Univariate analyses revealed that HIV+ individuals exhibited smaller brain volumes in the amygdala $F(1, 192) = 11.28$, $p < 0.01$, $\eta_p^2 = 0.06$), putamen $F(1, 192) = 11.69$, $p < 0.01$, $\eta_p^2 = 0.06$), corpus callosum $F(1, 192) = 4.60$, $p = 0.03$, $\eta_p^2 = 0.02$), and hippocampus ($F(1, 192) = 16.44$, $p < 0.01$, $\eta_p^2 = 0.08$) when compared to HIV- controls.

All significant differences among individual brain regions survived FDR correction for multiple comparisons. There was no significant main effect of ELS on brain volumes (Wilks' $\Lambda = 0.98$, $F(6, 187) = 0.62$, $p = 0.72$, $\eta_p^2 = 0.02$; Table 3).

No significant HIV x ELS interaction was observed on executive function (Wilks' $\Lambda = 0.98$, $F(4, 191) = 0.79$, $p = 0.53$, $\eta_p^2 = 0.02$). However, results revealed a significant main effect for HIV on executive function (Wilks' $\Lambda = 0.93$, $F(4, 191) = 3.63$, $p < 0.01$, $\eta_p^2 = 0.07$). Univariate results revealed that HIV+ individuals performed worse on Trial 3 of the CWIT ($F(1, 191) = 12.36$, $p < 0.01$, $\eta_p^2 = 0.06$), LNS ($F(1, 191) = 4.66$, $p = 0.03$, $\eta_p^2 = 0.02$), and verb fluency ($F(1, 191) = 5.87$, $p = 0.02$, $\eta_p^2 = 0.03$) when compared to HIV- individuals. All significant differences among individual tests survived FDR correction for multiple comparisons. There was no significant main effect for ELS on executive function (Wilks' $\Lambda = 0.96$, $F(4, 191) = 1.90$, $p = 0.11$, $\eta_p^2 = 0.04$). Additionally, there was no significant HIV x ELS interaction for psychomotor/processing speed (Wilks' $\Lambda = 0.96$, $F(4, 187) = 1.99$, $p = 0.10$, $\eta_p^2 = 0.04$). There were also no significant main effects of HIV (Wilks' $\Lambda = 0.98$, $F(4, 187) = 1.11$, $p = 0.35$, $\eta_p^2 = 0.02$) or ELS (Wilks' $\Lambda = 0.98$, $F(4, 187) = 0.89$, $p = 0.47$, $\eta_p^2 = 0.02$) on psychomotor/processing speed. Furthermore, no significant HIV x ELS interaction was observed on learning ($F(1, 199) = 0.07$, $p = 0.80$, $\eta_p^2 < 0.01$). Additionally, there was no significant main effect of HIV ($F(1, 199) = 2.43$, $p = 0.12$, $\eta_p^2 = 0.01$) or ELS ($F(1, 199) = 0.03$, $p = 0.87$, $\eta_p^2 < 0.01$; Table 4) on learning. Overall, no significant HIV x ELS interactions were observed on DTI metrics, brain volumes, or neuropsychological performance. Therefore, regressions examining the relationship between white matter integrity in specific tracts of interest and brain volumes with cognition were not examined.

Exploratory Aims

Exploratory Aim 1: No significant HIV x ELS interaction was observed on whole-brain FA. However, results revealed significant main effects for HIV on FA ($p < 0.05$; Figure 1), with lower FA in HIV+ individuals. Additionally, there was a significant main effect for ELS on FA ($p < 0.05$; Figure 2), with individuals in the high ELS exhibiting lower FA than individuals with low ELS. There was no significant HIV x ELS interaction for whole-brain RD. However, a trend level main effect for HIV on RD was observed ($p = 0.08$), with higher RD in HIV+ individuals, particularly in areas of the temporal lobe and external capsule (Figure 3). Additionally, a main effect for ELS on RD was observed at a trend level ($p = 0.09$), with individuals with high ELS exhibiting higher RD than individuals with low ELS, particularly in areas of the frontal lobes (Figure 4). There was no significant HIV x ELS interaction on whole-brain AD. Furthermore, no significant main effects for HIV or ELS were observed on AD. Mean skeletal values for DTI metrics are included in Supplemental Table 3.

Exploratory Aim 2: The average number of ELS events in the HIV+ group was 4.14 ($SD = 2.91$; Range 0-14). Linear regressions examining the relationship between DTI metrics and number of ELS events identified no significant relationships with FA values ($F(4, 123) = 0.90, p = 0.46, f^2 = 0.03$), AD values ($F(4, 120) = 1.73, p = 0.15, f^2 = 0.06$), or RD values ($F(4, 121) = 0.84, p = 0.50, f^2 = 0.03$). Additionally, there were no significant relationships observed between the number of ELS events and brain volumes ($F(7, 126) = 0.77, p = 0.61, f^2 = 0.04$). Lastly, no significant relationships were evident between the number of ELS events and tests of executive function ($F(4, 115) = 0.76, p = 0.55, f^2 = 0.03$), psychomotor/processing speed ($F(4, 117) = 1.15, p = 0.34, f^2 = 0.04$), or

learning ($r = 0.09$, $p = 0.31$).

Exploratory Aim 3: There were no significant differences between HIV+ individuals that reported abuse and/or neglect ($n = 64$) and those that did not report abuse and/or neglect ($n = 67$) on FA values (Wilks' $\Lambda = 0.99$, $F(1, 126) = 0.38$, $p = 0.82$, $\eta_p^2 = 0.01$), AD values (Wilks' $\Lambda = 0.73$, $F(4, 123) = 0.73$, $p = 0.57$, $\eta_p^2 = 0.02$), or RD values (Pillai's Trace = 0.01, $F(4, 121) = 0.44$, $p = 0.78$, $\eta_p^2 = 0.01$). No significant differences between groups were observed for brain volumes (Wilks' $\Lambda = 0.99$, $F(6, 119) = 0.14$, $p = 0.99$, $\eta_p^2 = 0.01$). Lastly, executive function (Wilks' $\Lambda = 0.99$, $F(4, 123) = 0.38$, $p = 0.82$, $\eta_p^2 = 0.01$), psychomotor/processing speed (Wilks' $\Lambda = 0.98$, $F(4, 117) = 0.73$, $p = 0.57$, $\eta_p^2 = 0.02$), and learning ($F(1, 129) = 1.48$, $p = 0.23$, $\eta_p^2 = 0.01$) performance did not differ between the two groups.

Exploratory Aim 4: No significant HIV x ELS interaction was observed for FA (Wilks' $\Lambda = 0.99$, $F(4, 174) = 0.09$, $p = 0.99$, $\eta_p^2 < 0.01$), AD (Wilks' $\Lambda = 0.99$, $F(4, 171) = 0.48$, $p = 0.75$, $\eta_p^2 = 0.01$), or RD (Pillai's Trace = 0.01, $F(4, 172) = 0.43$, $p = 0.78$, $\eta_p^2 = 0.01$) with high ELS defined by ≥ 3 ELS events and low ELS defined by < 2 ELS events. Additionally, no main effects of HIV were observed on FA (Wilks' $\Lambda = 0.99$, $F(4, 174) = 0.57$, $p = 0.68$, $\eta_p^2 = 0.01$), AD (Wilks' $\Lambda = 0.96$, $F(4, 171) = 1.87$, $p = 0.12$, $\eta_p^2 = 0.04$), or RD (Pillai's Trace = 0.01, $F(4, 172) = 0.38$, $p = 0.82$, $\eta_p^2 < 0.01$). There were also no main effects of ELS on FA (Wilks' $\Lambda = 0.99$, $F(4, 174) = 0.15$, $p = 0.96$, $\eta_p^2 < 0.01$), AD (Wilks' $\Lambda = 0.97$, $F(4, 171) = 1.21$, $p = 0.31$, $\eta_p^2 = 0.03$), or RD (Pillai's Trace = 0.02, $F(4, 172) = 0.67$, $p = 0.60$, $\eta_p^2 = 0.02$).

Similarly, no HIV x ELS interaction was observed on brain volumes (Wilks' $\Lambda = 0.99$, $F(6, 169) = 0.21$, $p = 0.97$, $\eta_p^2 < 0.01$). However, there was a significant main effect

of HIV on brain volumes (Wilks' $\Lambda = 0.92$, $F(6, 169) = 2.62$, $p = 0.20$, $\eta_p^2 = 0.09$).

Univariate analyses revealed that HIV+ individuals exhibited smaller brain volumes in the amygdala ($F(1, 174) = 8.67$, $p < 0.01$, $\eta_p^2 = 0.05$), putamen ($F(1, 174) = 9.39$, $p < 0.01$, $\eta_p^2 = 0.05$), and hippocampus ($F(1, 174) = 10.98$, $p < 0.01$, $\eta_p^2 = 0.06$) when compared to HIV- controls. All significant differences among individual brain regions survived FDR correction for multiple comparisons. There was no significant main effect of ELS on brain volumes (Wilks' $\Lambda = 0.98$, $F(6, 167) = 0.65$, $p = 0.69$, $\eta_p^2 = 0.02$).

Lastly, no significant HIV x ELS interaction was observed on executive function (Wilks' $\Lambda = 0.97$, $F(4, 168) = 1.15$, $p = 0.33$; $\eta_p^2 = 0.03$). However, results revealed a significant main effect for HIV on executive function (Wilks' $\Lambda = 0.92$, $F(4, 168) = 2.49$, $p < 0.01$, $\eta_p^2 = 0.08$). Univariate results revealed that HIV+ individuals performed worse on Trial 3 of the CWIT ($F(1, 171) = 9.48$, $p < 0.01$, $\eta_p^2 = 0.05$), LNS ($F(1, 171) = 4.69$, $p = 0.03$, $\eta_p^2 = 0.03$), and verb fluency ($F(1, 171) = 6.68$, $p = 0.03$, $\eta_p^2 = 0.04$) when compared to HIV- individuals. All significant differences among individual tests survived FDR correction for multiple comparisons. There was no significant main effect for ELS on executive function (Wilks' $\Lambda = 0.97$, $F(4, 168) = 1.30$, $p = 0.26$, $\eta_p^2 = 0.03$). Additionally, there was no significant HIV x ELS interaction for psychomotor/processing speed (Wilks' $\Lambda = 0.97$, $F(4, 166) = 1.49$, $p = 0.21$, $\eta_p^2 = 0.04$). There were also no significant main effects of HIV (Wilks' $\Lambda = 0.98$, $F(4, 166) = 0.99$, $p = 0.41$, $\eta_p^2 = 0.02$) or ELS (Wilks' $\Lambda = 0.98$, $F(4, 166) = 0.78$, $p = 0.54$, $\eta_p^2 = 0.02$) on psychomotor/processing speed. Furthermore, no significant HIV x ELS interaction was observed on learning ($F(1, 184) = 0.005$, $p = 0.95$, $\eta_p^2 < 0.01$). Additionally, there was no significant main effect of HIV on learning ($F(1, 184) = 1.14$, $p = 0.29$, $\eta_p^2 < 0.01$) or ELS

($F(1, 184) = 0.09, p = 0.77, \eta_p^2 < 0.01$).

Discussion

The primary goal of this research was to determine if high ELS contributes to brain structural and cognitive abnormalities in HIV+ individuals. There were no significant interactions between HIV and ELS on neuroimaging outcomes or neuropsychological performance. However, results revealed significantly greater whole-brain white matter microstructural abnormalities, smaller brain volumes, and lower cognition in HIV+ individuals when compared to HIV– controls. Individuals with high ELS also demonstrated greater whole-brain white matter microstructural abnormalities compared to individuals with low ELS, independent of HIV serostatus. Neither HIV nor high ELS was associated with white matter tract abnormalities in the uncinate fasciculus, cingulum bundle, or corpus callosum. Collectively, findings from the present study do not suggest that high ELS is a major contributor to brain dysfunction in HIV+ individuals on HAART.

Co-morbid HIV and ELS and Neuroimaging and Cognitive Outcomes

Studies have revealed that ELS may contribute to HIV-related gray matter abnormalities (Spies et al., 2016) and reduced neuropsychological performance (Clark et al., 2012; Spies et al., 2016). Furthermore, white matter abnormalities have been observed in individuals with HIV (e.g., Fillippi et al., 2001; Heaps-Woodruff et al., 2016, Paul et al., 2016; Wu et al., 2006) and ELS (e.g., Choi et al., 2009; Huang et al., 2012; Lu et al., 2013; Paul et al., 2008; Seckfort et al., 2008), independently. Therefore, it was predicted that ELS would contribute to HIV-related abnormalities in gray matter volumes, white matter microstructural integrity, and neuropsychological performance. In

contrast to the proposed hypotheses, results did not reveal a significant interaction between HIV and ELS on brain integrity. Exploratory findings also did not suggest that co-morbid HIV and high ELS was associated with HIV-related brain dysfunction using multiple methods to quantify ELS events (i.e., total number of ELS events experienced, prior abuse and/or neglect, or low ELS defined by < 2 ELS events on ELSQ).

These findings differ from data presented in previous studies of co-morbid HIV and ELS on brain integrity (Clark et al., 2012, Spies et al., 2016). Importantly, the most robust negative effects of HIV and ELS were observed in a cohort of HIV+ individuals with limited HAART use (< 50%; Spies et al., 2016), whereas all individuals in the present study were on HAART. The HIV+ group in Spies et al. (2016) exhibited a notably higher viral load ($M = 116,172$ copies/ml, range = < 20-3,200,000 copies/ml, % undetectable viral load not reported) and a lower CD4 T-cell count ($M = 431$ cells/ μ l, range = 25-1,529 cells/ μ l), on average, compared to individuals in the present study (viral load $M = 2,069$ copies/ml, range = < 20-2,069 copies/ml, 81% undetectable viral load; CD4 T-cell count $M = 601$ cells/ μ l, range = 56-1,462 cells/ μ l). Therefore, it is possible that the negative effect of ELS in HIV+ individuals may emerge in the context of greater immunosuppression and is not present in individuals with largely suppressed viremia. Future longitudinal studies examining co-morbid HIV and ELS on brain integrity pre- and post-HAART use may help to elucidate this possibility.

HIV on Neuroimaging and Cognitive Outcomes

The HIV+ group exhibited significantly greater global white matter abnormalities compared with HIV- controls in the absence of pronounced differences in the localized tracts examined (i.e., uncinate fasciculus, cingulum bundle, corpus callosum), suggesting

subtle white matter injury widely distributed throughout the brain. A similar widespread pattern of white matter abnormalities has been observed in individuals on antiretroviral therapy and with suppressed viremia (Nir et al., 2014; Su et al., 2016; Underwood et al., 2017). Specifically, HIV+ individuals in the present study exhibited significantly lower global FA and higher global RD, at a trend level, compared to HIV– individuals, with the most robust differences in RD evident in the temporal lobes and external capsule. This pattern of altered DTI metrics (low FA, high RD) has previously been observed in HIV+ individuals (Leite et al., 2013; Li et al., 2015; Underwood et al., 2017) and possibly reflects pronounced demyelination (Song et al., 2002). However, more recent research indicates a complex interpretation in which RD may be considered a marker of both axon and myelin integrity (Madden et al., 2012). Overall, these results extend findings of prior studies demonstrating whole-brain white matter injury in HAART-treated HIV+ individuals.

Results revealed evidence of residual gray matter and cognitive abnormalities in HIV+ individuals on HAART. Consistent with prior research, (Ances et al., 2006, 2012; Behrman-Lay et al., 2016; Baker et al., 2015; Becker et al., 2012; Paul et al., 2016; Sanford et al., 2017), HIV+ individuals demonstrated significantly lower volumes of the putamen, amygdala, corpus callosum, and hippocampus compared with HIV– controls. In terms of cognition, the HIV+ group exhibited a greater rate of cognitive impairment (33%) compared with the HIV– group (24%), an observation driven by lower executive performance in HIV+ individuals. Specifically, a significant main effect of HIV serostatus on executive function was observed, with HIV+ individuals performing significantly worse on Trial 3 of the CWIT, LNS, and Verb Fluency compared with HIV–

controls. These findings are similar to previous research demonstrating executive dysfunction in HIV+ individuals despite successful viral suppression (Antinori et al., 2007; Baker et al., 2015; Heaton et al., 2010; Woods et al., 2009). Collectively, these outcomes underscore the chronic nature of brain and cognitive dysfunction associated with HIV and suggest the need for interventions, such as cognitive rehabilitation (Becker et al., 2012), among HIV+ individuals on HAART to improve executive function.

ELS, Neuroimaging, and Cognitive Outcomes

In contrast to some previous studies (Choi et al., 2009; Lu et al., 2013; Poletti et al., 2015; Paul et al., 2008; Seckfort et al., 2008; Wu et al., 2006), results did not reveal localized disruption to the uncinate fasciculus, cingulum bundle, or corpus callosum in individuals with high ELS. However, the high ELS group exhibited significantly lower whole-brain FA and higher whole-brain RD, at a trend level, compared with the low ELS group, likely indicating diffuse disruption to axonal and myelin integrity (Madden et al., 2012). Results revealed the most prominent abnormalities in individuals with high ELS were localized to the frontal lobe (Figures 2 and 4). Inflammation may be one of many important drivers of these abnormalities in individuals with ELS (Fagundes & Way 2014; Kiecolt-Glaser et al., 2011; Raposa, Bower, Hammen, Najman, & Brennan, 2014). Chronic inflammation is common in individuals with ELS and may be due to increased cortisol production in response to stressors (van der Vegt, van der Ende, Kirschbaum, Verhulst, & Tiemeier, 2009). The persistence of high cortisol levels can lead to the production of proinflammatory cytokines, which affect synaptic production, axonal pruning, and myelination (reviewed in Glaser, 2000; Gunnar and Ouevedo, 2008). It has been suggested that the frontal lobe is particularly vulnerable to the effects of

inflammation due to protracted postnatal development, a high density of glucocorticoid receptors, and postnatal neurogenesis (Gogtay et al., 2004; Teicher et al., 2003).

There were no significant differences in brain volumes between individuals with high and low ELS, suggesting that the impact of high ELS may not be severe enough to induce gross morphological changes in this cohort. These data are consistent with prior work in co-morbid HIV and ELS (Clark et al., 2012), yet are inconsistent with the many studies demonstrating volumetric atrophy in the context of ELS, even in the absence of psychopathology in adulthood (Andersen et al., 2008; Baker et al., 2013; Cohen et al., 2006a; Korgaonkar et al., 2013; Saleh, Potter, McQuoid, & Boyd, 2016). It is possible that the method used to define low ELS (< 3 on the ELSQ in primary analyses and < 2 ELS events on the ELSQ in secondary analyses) may have contributed to the lack of significant differences observed between high and low ELS groups. Importantly, the most robust brain volume differences in adults without psychopathology were observed between individuals with no ELS (0 ELS events on the ELSQ) compared to individuals with high ELS (≥ 3 ELS events on the ELSQ; Cohen et al., 2006a). However, this method was not feasible in the present study, given insufficient power resulting from a low rate of individuals that reported no ELS exposure (11% in HIV+ group, 7% in HIV- group).

It is also possible that genetic variants of particular genes may contribute to the vulnerability or resilience of brain integrity in the context of early life stressors. Previous research has suggested that the influence of ELS on brain volumes in adulthood is partially moderated by risk alleles of the serotonin transporter (5-HTTLPR; Frodl et al., 2010a), the glutamate transporter polymorphism SLC1A2-181A>C (Poletti et al., 2014), and the brain-derived neurotrophic factor Val66Met (Carballedo et al., 2013; Gatt et al.,

2009) genetic polymorphisms in adults with and without psychopathology. Therefore, differences in genetics may have contributed the findings in the present study, however these relationships could not be assessed, as genotyping was not conducted. Nevertheless, future studies should continue to elucidate genetic and environment modifiers of ELS on brain integrity.

Individuals with high ELS did not exhibit lower neuropsychological performance when compared to individuals with low ELS, regardless of HIV serostatus. These results are consistent with some prior work in adults without psychopathology (Seckfort et al., 2008). Importantly, a majority of the studies demonstrating a significant relationship between ELS and cognition have consisted of participants with PTSD, MDD, and schizophrenia (Bremner et al., 2004; Gould et al., 2012; Lysaker et al., 2001; Navalta et al., 2006; Saleh et al., 2017; Shannon et al., 2009). The present findings, in conjunction with some previous research, suggest that cognitive dysfunction associated with ELS may not be evident on formal neuropsychological measures in the absence of psychopathology. However, it is also possible that the specific neuropsychological tests used in the present study contributed to the lack of significant differences. While the neuropsychological tests administered were sensitive to effects of HIV (Carey et al., 2004; Woods et al., 2005a), the battery was not designed to measure cognitive outcomes of co-morbid HIV and ELS. Prior studies in ELS have demonstrated that more complex measures, such as the California Verbal Learning Test-II (Delis, Kramer, Kaplan, & Ober, 2000) and the Wisconsin Card Sorting Test (Heaton, Chelune, Talley, Kay, & Curtis, 1992) are sensitive to the effects of ELS (Aas et al., 2011, Lyasker et al., 2001; Spies et al., 2017). As such, it remains unknown whether the behavioral phenotype

related to ELS would have been captured utilizing a larger and more comprehensive neuropsychological battery.

Conclusions should be tempered by several limitations. Retrospective self-reports of ELS are subject to recall bias (Hardt & Rutter, 2004). While significant effects of high ELS were identified in brain white matter, it remains unknown whether that the absence of an HIV and ELS interaction was influenced by the use of a retrospective ELS assessment. Therefore, prospective studies of the effects of ELS on brain integrity may be preferable in future studies. It is also possible that the salience and intensity of early adverse events influenced outcomes in the present study (Cohen et al., 2006b), however these elements are not included in the ELSQ. Accordingly, an assessment of ELS capturing these specific details is warranted. Furthermore, the HIV+ groups differed with respect to age and sex, such that the HIV+ group, on average, was significantly older than the HIV- group and consisted of more male participants. Although age and sex were controlled in analyses, it remains possible that these demographic differences may have had an indirect influence on the findings. Lastly, the current study utilized a cross-sectional study design and future longitudinal studies would allow for a more direct observation of the effects of HIV and ELS on brain integrity.

Conclusion

There is high rate of variability in HIV-related brain dysfunction. Although prior research has demonstrated that ELS may contribute to this variability, there were no significant HIV and ELS interactions on white matter microstructural integrity, brain volumes, or cognition in the present study. Overall, these data indicate that ELS does not represent a primary driver of the neuropathogenic model of HIV in the HAART era.

Nevertheless, persistent negative effects of HIV and high ELS on brain integrity were observed, which is consistent with prior research. Future studies are needed to confirm the interaction of HIV and ELS along the HIV disease continuum and to further elucidate the individual impact of HIV and ELS on health and wellness.

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References

- Aas, M., Djurovic, S., Athanasiu, L., Steen, N. E., Agartz, I., Lorentzen, S., ... & Melle, I. (2011). Serotonin transporter gene polymorphism, childhood trauma, and cognition in patients with psychotic disorders. *Schizophrenia Bulletin*, sbr113.
- Aas, M., Steen, N. E., Agartz, I., Aminoff, S. R., Lorentzen, S., Sundet, K., ... & Melle, I. (2012). Is cognitive impairment following early life stress in severe mental disorders based on specific or general cognitive functioning? *Psychiatry Research*, 198(3), 495-500.
- Aisa, B., Tordera, R., Lasheras, B., Del Río, J., & Ramírez, M. J. (2007). Cognitive impairment associated to HPA axis hyperactivity after maternal separation in rats. *Psychoneuroendocrinology*, 32(3), 256-266.
- Alexander, A. L., Lee, J. E., Lazar, M., & Field, A. S. (2007). Diffusion tensor imaging of the brain. *Neurotherapeutics*, 4(3), 316-329.
- American Psychiatric Association. (1994). DSM-IV: Diagnostic and statistical manual of mental disorders. *American Psychiatric Association, Washington DC*.
- Ances, B. M., Ortega, M., Vaida, F., Heaps, J., & Paul, R. (2012). Independent effects of HIV, aging, and HAART on brain volumetric measures. *Journal of Acquired Immune Deficiency Syndromes*, 59(5), 469-477.
- Ances, B. M., Roc, A. C., Wang, J., Korczykowski, M., Okawa, J., Stern, J., . . . Detre, J. A. (2006). Caudate blood flow and volume are reduced in HIV+ neurocognitively impaired patients. *Neurology*, 66(6), 862-866.

- Anda, R. F., Whitfield, C. L., Felitti, V. J., Chapman, D., Edwards, V. J., Dube, S. R., & Williamson, D. F. (2002). Adverse childhood experiences, alcoholic parents, and later risk of alcoholism and depression. *Psychiatric Services, 53*(8), 1001-1009.
- Andersen, S. L., Tomada, A., Vincow, E. S., Valente, E., Polcari, A., & Teicher, M. H. (2008). Preliminary evidence for sensitive periods in the effect of childhood sexual abuse on regional brain development. *Journal of Neuropsychiatry and Clinical Neurosciences, 20*(3), 292-301.
- Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., ... & Gisslén, M. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology, 69*(18), 1789-1799.
- Avital, A., Ram, E., Maayan, R., Weizman, A., & Richter-Levin, G. (2006). Effects of early-life stress on behavior and neurosteroid levels in the rat hypothalamus and entorhinal cortex. *Brain Research Bulletin, 68*(6), 419-424.
- Baker, L. M., Cooley, S., Cabeen, R. P., Laidlaw, D. H., Joska, J. A., Hoare, J., ... & Paul, R. H. (2017). Topological organization of whole-brain white matter in HIV infection. *Brain Connectivity, (ja)*.
- Baker, L. M., Paul, R. H., Heaps, J. M., Westerhaus, E., Chang, J. Y., Williams, S., & ... Ances, B. M. (2014). Impact of human immunodeficiency virus on neurocognition and risky behaviors in young adults. *Journal of NeuroVirology, 20*(5), 466-473.
- Baker, L. M., Paul, R. H., Heaps-Woodruff, J. M., Chang, J. Y., Ortega, M., Margolin, Z., ... & Ances, B. M. (2015). The effect of central nervous system penetration effectiveness of highly active antiretroviral therapy on neuropsychological

performance and neuroimaging in HIV infected individuals. *Journal of Neuroimmune Pharmacology*, 10(3), 487-492.

Baker, L. M., Williams, L. M., Korgaonkar, M. S., Cohen, R. A., Heaps, J. M., & Paul, R. H. (2013). Impact of early vs. late childhood early life stress on brain morphometrics. *Brain Imaging and Behavior*, 7(2), 196-203.

Basser, P.J., & Pierpaoli, C. (1996). Microstructural features measured using diffusion tensor imaging. *Journal of Magnetic Resonance, Series B*, 111(3), 209-219.

Beck A.T., Steer R.A., & Brown G.K. (1996). *Manual for the Beck Depression Inventory-II*. San Antonio, TX: Psychological Corporation.

Becker, J. T., Dew, M. A., Aizenstein, H. J., Lopez, O. L., Morrow, L., Saxton, J., & Tárraga, L. (2012). A pilot study of the effects of internet-based cognitive stimulation on neuropsychological function in HIV disease. *Disability and Rehabilitation*, 34(21), 1848-1852.

Becker, J. T., Sanders, J., Madsen, S. K., Ragin, A., Kingsley, L., Maruca, V., ... & Sacktor, N. (2011). Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging and Behavior*, 5(2), 77-85.

Becker, J. T., Lopez, O. L., Dew, M. A., & Aizenstein, H. J. (2004). Prevalence of cognitive disorders differs as a function of age in HIV virus infection. *AIDS*, 18, 11-18.

Behrman-Lay, A. M., Paul, R. H., Heaps-Woodruff, J., Baker, L. M., Usher, C., & Ances, B. M. (2016). Human immunodeficiency virus has similar effects on brain volumetrics and cognition in males and females. *Journal of NeuroVirology*, 22(1), 93-103.

- Benedetti, F., Bollettini, I., Radaelli, D., Poletti, S., Locatelli, C., Falini, A., ... & Colombo, C. (2014). Adverse childhood experiences influence white matter microstructure in patients with bipolar disorder. *Psychological Medicine*, *44*(14), 3069-3082.
- Benedict, R. H., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test—Revised: Normative data and analysis of inter-form and test-retest reliability. *The Clinical Neuropsychologist*, *12*(1), 43-55.
- Benjamini, Y., & Hochberg, Y. (1995). Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. *Journal of the Royal Statistical Society. Series B (Methodological)*, *57*(1), 289-300.
- Bernstein, D. P., Stein, J. A., Newcomb, M. D., Walker, E., Pogge, D., Ahluvalia, T., & ... Zule, W. (2003). Development and validation of a brief screening version of the Childhood Trauma Questionnaire. *Child Abuse & Neglect*, *27*(2), 169-190.
- Brandt, J., & Benedict, R. H. (2001). *Hopkins verbal learning test--revised: professional manual*. Psychological Assessment Resources.
- Bremner, J. D., Vermetten, E., Afzal, N., & Vythilingam, M. (2004). Deficits in verbal declarative memory function in women with childhood sexual abuse-related posttraumatic stress disorder. *The Journal of Nervous and Mental Disease*, *192*(10), 643-649.
- Brunson, K. L., Kramár, E., Lin, B., Chen, Y., Colgin, L. L., Yanagihara, T. K., & ... Baram, T. Z. (2005). Mechanisms of Late-Onset Cognitive Decline after Early-Life Stress. *The Journal of Neuroscience*, *25*(41), 9328-9338.

- Carballedo, A., Morris, D., Zill, P., Fahey, C., Reinhold, E., Meisenzahl, E., ... & Frodl, T. (2013). Brain- derived neurotrophic factor Val66Met polymorphism and early life adversity affect hippocampal volume. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 162(2), 183-190.
- Carey, C. L., Woods, S. P., Gonzalez, R., Conover, E., Marcotte, T. D., Grant, I., & Heaton, R. K. (2004). Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. *Journal of Clinical and Experimental Neuropsychology*, 26(3), 307-319.
- Chaney, A., Carballedo, A., Amico, F., Fagan, A., Skokauskas, N., Meaney, J., & Frodl, T. (2014). Effect of childhood maltreatment on brain structure in adult patients with major depressive disorder and healthy participants. *Journal of Psychiatry & Neuroscience*, 39(1), 50.
- Charlton, R. A., Barrick, T. R., McIntyre, D. J., Shen, Y., O'sullivan, M., Howe, F. E. E. A., ... & Markus, H. S. (2006). White matter damage on diffusion tensor imaging correlates with age-related cognitive decline. *Neurology*, 66(2), 217-222.
- Chen, Y., An, H., Zhu, H., Stone, T., Smith, J. K., Hall, C., & ... Lin, W. (2009). White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients. *Neuroimage*, 47(4), 1154-1162.
- Cherner, M., Letendre, S., Heaton, R. K., Durrelle, J., Marquie-Beck, J., Gragg, B., ... & HIV Neurobehavioral Research Center Group. (2005). Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. *Neurology*, 64(8), 1343-1347.

- Choi, J., Jeong, B., Rohan, M. L., Polcari, A. M., & Teicher, M. H. (2009). Preliminary evidence for white matter tract abnormalities in young adults exposed to parental verbal abuse. *Biological Psychiatry*, 65(3), 227-234.
- Choi, J., Jeong, B., Polcari, A., Rohan, M. L., & Teicher, M. H. (2012). Reduced fractional anisotropy in the visual limbic pathway of young adults witnessing domestic violence in childhood. *Neuroimage*, 59(2), 1071-1079.
- Cicchetti, D. (2004). An Odyssey of Discovery: Lessons learned through three decades of research on child maltreatment. *American Psychologist*, 59(8), 731-741.
- Clark, U. S., Cohen, R. A., Sweet, L. H., Gongvatana, A., Devlin, K. N., Hana, G. N., & ... Tashima, K. T. (2012). Effects of HIV and early life stress on amygdala morphometry and neurocognitive function. *Journal of The International Neuropsychological Society*, 18(4), 657-668.
- Clark, U. S., Sweet, L. H., Morgello, S., Philip, N. S., & Cohen, R. A. (2016). High early life stress and aberrant amygdala activity: Risk factors for elevated neuropsychiatric symptoms in HIV+ adults. *Brain Imaging and Behavior*, 1-17.
- Cloak, C. C., Chang, L., & Ernst, T. (2004). Increased frontal white matter diffusion is associated with glial metabolites and psychomotor slowing in HIV. *Journal of Neuroimmunology*, 157(1), 147-152.
- Cohen, R. A., Grieve, S., Hoth, K. F., Paul, R. H., Sweet, L., Tate, D., ... & Niaura, R. (2006a). Early life stress and morphometry of the adult anterior cingulate cortex and caudate nuclei. *Biological Psychiatry*, 59(10), 975-982.
- Cohen, R. A., Hitsman, B. L., Paul, R. H., McCaffery, J., Stroud, L., Sweet, L., & ... Gordon, E. (2006b). Early life stress and adult emotional experience: An

international perspective. *International Journal of Psychiatry In Medicine*, 36(1), 35-52.

- Cohen, R. A., Seider, T. R., & Navia, B. (2015). HIV effects on age-associated neurocognitive dysfunction: premature cognitive aging or neurodegenerative disease? *Alzheimer's Research & Therapy*, 7(1), 37.
- Dale, A. M., Fischl, B., & Sereno, M. I. (1999). Cortical surface-based analysis: I. Segmentation and surface reconstruction. *Neuroimage*, 9(2), 179-194.
- Davis, S. W., Dennis, N. A., Buchler, N. G., White, L. E., Madden, D. J., & Cabeza, R. (2009). Assessing the effects of age on long white matter tracts using diffusion tensor tractography. *Neuroimage*, 46(2), 530-541.
- De Bellis, M. D., & Keshavan, M. S. (2003). Sex differences in brain maturation in maltreatment-related pediatric posttraumatic stress disorder. *Neuroscience and Biobehavioral Reviews*, 27(1-2), 103-117.
- Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). D-KEFS: examiners manual. *San Antonio, TX: The Psychological Corporation.*
- Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *CVLT-II: California verbal learning test: adult version*. Psychological Corporation.
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... & Albert, M. S. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *Neuroimage*, 31(3), 968-980.
- Devlin, K. N., Gongvatana, A., Clark, U. S., Chasman, J. D., Westbrook, M. L., Tashima, K. T., & ... Cohen, R. A. (2012). Neurocognitive effects of HIV, hepatitis C, and

substance use history. *Journal of The International Neuropsychological Society*, 18(1), 68-78.

Diao, L., Yu, H., Zheng, J., Chen, Z., Huang, D., & Yu, L. (2015). Abnormalities of the uncinate fasciculus correlate with executive dysfunction in patients with left temporal lobe epilepsy. *Magnetic Resonance Imaging*, 33(5), 544-550.

Dong, M., Giles, W. H., Felitti, V. J., Dube, S. R., Williams, J. E., Chapman, D. P., & Anda, R. F. (2004). Insights into causal pathways for ischemic heart disease: Adverse childhood experiences study. *Circulation*, 110(13), 1761-1766.

Edwards, V. J., Holden, G. W., Felitti, V. J., & Anda, R. F. (2003). Relationship between multiple forms of childhood maltreatment and adult mental health in community respondents: Results from the Adverse Childhood Experiences study. *The American Journal of Psychiatry*, 160(8), 1453-1460.

Egger, M., Hirschel, B., Francioli, P., Sudre, P., Wirz, M., Flepp, M., . . . Battegay, M. (1997). Impact of new antiretroviral combination therapies in HIV infected patients in Switzerland: Prospective multicentre study. *British Medical Journal*, 315(7117), 1194-1199.

Ellis, R. J., Badiee, J., Vaida, F., Letendre, S., Heaton, R. K., Clifford, D., ... & McCutchan, J. A. (2011). CD4 nadir is a predictor of HIV neurocognitive impairment in the era of combination antiretroviral therapy. *AIDS*, 25(14).

Enoch, M. (2011). The role of early life stress as a predictor for alcohol and drug dependence. *Psychopharmacology*, 214(1), 17-31.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in Cognitive Sciences*, 15(2), 85-93.

- Fagundes, C. P., & Way, B. (2014). Early-life stress and adult inflammation. *Current Directions in Psychological Science*, 23(4), 277-283.
- Filippi, C. G., Ulu, A. M., Ryan, E., Ferrando, S. J., & van Gorp, W. (2001). Diffusion tensor imaging of patients with HIV and normal-appearing white matter on MR images of the brain. *American Journal of Neuroradiology*, 22(2), 277-283.
- Fischl, B., Sereno, M. I., & Dale, A. M. (1999). Cortical surface-based analysis: II. inflation, flattening, and a surface-based coordinate system. *Neuroimage*, 9(2), 195-207.
- Fischl, B., Van Der Kouwe, A., Destrieux, C., Halgren, E., Ségonne, F., Salat, D. H., ... Dale, A. M. (2004). Automatically parcellating the human cerebral cortex. *Cerebral Cortex*, 14(1), 11-22.
- Friedman, M. A., Schinka, J. A., Mortimer, J. A., & Graves, A. B. (2002). Hopkins verbal learning test—revised: Norms for elderly African Americans. *The Clinical Neuropsychologist*, 16(3), 356-372.
- Frodl, T., Carballedo, A., Fagan, A. J., Lisiecka, D., Ferguson, Y., & Meaney, J. F. (2012). Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression. *Journal of Psychiatry & Neuroscience*, 37(1), 37-45.
- Frodl, T., Reinhold, E., Koutsouleris, N., Donohoe, G., Bondy, B., Reiser, M., ... & Meisenzahl, E. M. (2010). Childhood stress, serotonin transporter gene and brain structures in major depression. *Neuropsychopharmacology*, 35(6), 1383-1390.
- Gatt, J. M., Nemeroff, C. B., Dobson-Stone, C., Paul, R. H., Bryant, R. A., Schofield, P. R., ... & Williams, L. M. (2009). Interactions between BDNF Val66Met

polymorphism and early life stress predict brain and arousal pathways to syndromal depression and anxiety. *Molecular Psychiatry*, 14(7), 681-695.

Glaser, D. (2000). Child abuse and neglect and the brain-A review. *The Journal of Child Psychology and Psychiatry and Allied Disciplines*, 41(1), 97-116.

Gogtay, N., Giedd, J. N., Lusk, L., Hayashi, K. M., Greenstein, D., Vaituzis, A. C., ... & Rapoport, J. L. (2004). Dynamic mapping of human cortical development during childhood through early adulthood. *Proceedings of the National Academy of Sciences of the United States of America*, 101(21), 8174-8179.

Gongvatana, A., Cohen, R. A., Correia, S., Devlin, K. N., Miles, J., Kang, H., & ... Tashima, K. T. (2011). Clinical contributors to cerebral white matter integrity in HIV-infected individuals. *Journal of NeuroVirology*, 17(5), 477-486.

Gongvatana, A., Schweinsburg, B. C., Taylor, M. J., Theilmann, R. J., Letendre, S. L., Alhassoon, O. M., & ... Grant, I. (2009). White matter tract injury and cognitive impairment in human immunodeficiency virus-infected individuals. *Journal of NeuroVirology*, 15(2), 187-195.

Gould, F., Clarke, J., Heim, C., Harvey, P. D., Majer, M., & Nemeroff, C. B. (2012). The effects of child abuse and neglect on cognitive functioning in adulthood. *Journal of Psychiatric Research*, 46(4), 500-506.

Grant, I. (2008). Neurocognitive disturbances in HIV. *International Review of Psychiatry*, 20(1), 33-47.

Gunnar, M. R., & Quevedo, K. M. (2008). Early care experiences and HPA axis regulation in children: A mechanism for later trauma vulnerability. *Progress in Brain Research*, 167, 137.

- Hardt, J., & Rutter, M. (2004). Validity of adult retrospective reports of adverse childhood experiences: Review of the evidence. *Journal of Child Psychology and Psychiatry*, 45(2), 260-273.
- Harezlak, J., Buchthal, S., Taylor, M., Schifitto, G., Zhong, J., Daar, E., & ... Navia, B. (2011). Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. *AIDS*, 25(5), 625-633.
- Harrison, P. A., Fulkerson, J. A., & Beebe, T. J. (1997). Multiple substance use among adolescent physical and sexual abuse victims. *Child Abuse & Neglect*, 21(6), 529-539.
- Heaps-Woodruff, J. M., Wright, P. W., Ances, B. M., Clifford, D., & Paul, R. H. (2016). The impact of human immune deficiency virus and hepatitis C coinfection on white matter microstructural integrity. *Journal of NeuroVirology*, 22(3), 389-399.
- Heaton, R. K., Chelune, G. J., Talley, J. L., Kay, G. G., & Curtis, G. (1992). Wisconsin Card Sorting Test (WCST). Manual Revised and Expanded. Odessa, Florida: Psychological Assessment Resources; 1993.
- Heaton, R. K., Clifford, D. B., Franklin, D. J., Woods, S. P., Ake, C., Vaida, F., & ... Grant, I. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: Charter study. *Neurology*, 75(23), 2087-2096.
- Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., LeBlanc, S., & ... Grant, I. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. *Journal of NeuroVirology*, 17(1), 3-16.

- Heaton, R. K., Miller, S. W., Taylor, M. J., & Grant, I. (2004). Revised comprehensive norms for an expanded Halstead-Reitan Battery: Demographically adjusted neuropsychological norms for African American and Caucasian adults. *Lutz, FL: Psychological Assessment Resources*.
- Hinkin, C. H., Castellon, S. A., Levine, A. J., Barclay, T. R., & Singer, E. J. (2008). Neurocognition in individuals co-infected with HIV and hepatitis C. *Journal of Addictive Diseases, 27*(2), 11-17.
- Hoare, J., Fouche, J. P., Spottiswoode, B., Donald, K., Philipps, N., Bezuidenhout, H., ... & Paul, R. (2012a). A diffusion tensor imaging and neurocognitive study of HIV-positive children who are HAART-naïve “slow progressors”. *Journal of NeuroVirology, 18*(3), 205-212.
- Hoare, J., Westgarth-Taylor, J., Fouche, J., Spottiswoode, B., Paul, R., Thomas, K., & ... Joska, J. (2012b). A diffusion tensor imaging and neuropsychological study of prospective memory impairment in South African HIV positive individuals. *Metabolic Brain Disease, 28*(4), 731.
- Hoth, K. F., Paul, R. H., Williams, L. M., Dobson-Stone, C., Todd, E., Schofield, P. R., & ... Gordon, E. (2006). Associations between the COMTVal/Met polymorphism, early life stress, and personality among healthy adults. *Neuropsychiatric Disease and Treatment, 2*(2), 219-225.
- Huang, H., Gundapuneedi, T., & Rao, U. (2012). White matter disruptions in adolescents exposed to childhood maltreatment and vulnerability to psychopathology. *Neuropsychopharmacology, 37*(12), 2693-2701.

- Jenkinson, M., & Smith, S. (2001). A global optimization method for robust affine registration of brain images. *Medical Image Analysis*, 5(2), 143-156.
- Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved optimization for the robust and accurate linear registration and motion correction of brain images. *Neuroimage*, 17(2), 825-841.
- Johnson, C. P., Juranek, J., Kramer, L. A., Prasad, M. R., Swank, P. R., & Ewing-Cobbs, L. (2011). Predicting behavioral deficits in pediatric traumatic brain injury through uncinate fasciculus integrity. *Journal of the International Neuropsychological Society*, 17(4), 663-673.
- Kiecolt-Glaser, J. K., Gouin, J., Weng, N., Malarkey, W. B., Beversdorf, D. Q., & Glaser, R. (2011). Childhood adversity heightens the impact of later-life caregiving stress on telomere length and inflammation. *Psychosomatic Medicine*, 73(1), 16-22.
- Kløve, H. (1963). Grooved pegboard. *Lafayette, IN: Lafayette Instruments*.
- Korgaonkar, M. S., Antees, C., Williams, L. M., Gatt, J. M., Bryant, R. A., Cohen, R., . . . Grieve, S. M. (2013). Early exposure to traumatic stressors impairs emotional brain circuitry: E75524. *PLoS One*, 8(9).
- Le Bihan, D., Mangin, J., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, 13(4), 534-546.
- Leite, S. C. B., Corrêa, D. G., Doring, T. M., Kubo, T. T. A., Netto, T. M., Ferracini, R., . . . Gasparetto, E. L. (2013). Diffusion tensor MRI evaluation of the corona radiata, cingulate gyri, and corpus callosum in HIV patients. *Journal of Magnetic Resonance Imaging*, 38(6), 1488-1493.

- Li, R., Tang, Z., Mi, H., Zhao, J., Yuan, D., & Li, H. (2015). Diffusion tensor imaging study of early white matter integrity in HIV-infected patients: A tract-based spatial statistics analysis. *Radiology of Infectious Diseases*, 2(4), 183-191.
- Lu, S., Wei, Z., Gao, W., Wu, W., Liao, M., Zhang, Y., . . . Li, L. (2013). White matter integrity alterations in young healthy adults reporting childhood trauma: A diffusion tensor imaging study. *The Australian and New Zealand Journal of Psychiatry*, 47(12), 1183.
- Lucas, J. A., Ivnik, R. J., Smith, G. E., Ferman, T. J., Willis, F. B., Petersen, R. C., & Graff-Radford, N. R. (2005). Mayo's older african americans normative studies: Norms for boston naming test, controlled oral word association, category fluency, animal naming, token test, wrat-3 reading, trail making test, stroop test, and judgment of line orientation. *The Clinical Neuropsychologist*, 19(2), 243-269.
- Lysaker, P. H., Meyer, P., Evans, J. D., & Marks, K. A. (2001). Neurocognitive and symptom correlates of self-reported childhood sexual abuse in schizophrenia spectrum disorders. *Annals of Clinical Psychiatry*, 13(2), 89-92.
- Madden, D. J., Bennett, I. J., Burzynska, A., Potter, G. G., Chen, N., & Song, A. W. (2012). Diffusion tensor imaging of cerebral white matter integrity in cognitive aging. *Biochimica Et Biophysica Acta - Molecular Basis of Disease*, 1822(3), 386-400.
- Majer, M., Nater, U. M., Lin, J. M. S., Capuron, L., & Reeves, W. C. (2010). Association of childhood trauma with cognitive function in healthy adults: a pilot study. *BMC Neurology*, 10(1), 61.

- McCutchan, J. A., Wu, J. W., Robertson, K., Koletar, S. L., Ellis, R. J., Cohn, S., ... & Williams, P. L. (2007). HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. *AIDS*, *21*(9), 1109-1117.
- McGee, R. A., Wolfe, D. A., Yuen, S. A., Wilson, S. K., & Carnochan, J. (1995). The measurement of maltreatment: A comparison of approaches. *Child Abuse & Neglect*, *19*(2), 233-249.
- McFarlane, A. C., Clark, R. R., Bryant, R., Williams, L., Niaura, R., Paul, R., . . . Gordon, E. (2005). The impact of early life stress on psychophysiological, personality and behavioral measures in 740 non-clinical subjects. *Journal of Integrative Neuroscience*, *4*(01), 27-40.
- Meaney, M. J., Mitchell, J. B., Aitken, D. H., Bhatnagar, S., Bodnoff, S. R., Iny, L. J., & Sarrieau, A. (1991). The effects of neonatal handling on the development of the adrenocortical response to stress: Implications for neuropathology and cognitive deficits in later life. *Psychoneuroendocrinology*, *16*(1-3), 85-103.
- Mori, S., Wakana, S., Nagee-Poetscher, L. M., & Van Zijl, P. C. M. (2005). MRI atlas of human white matter. *American Journal of Neuroradiology*, *27*(6), 1384.
- Müller-Oehring, E. M., Schulte, T., Rosenbloom, M. J., Pfefferbaum, A., & Sullivan, E. V. (2010). Callosal degradation in HIV-1 infection predicts hierarchical perception: A DTI study. *Neuropsychologia*, *48*(4), 1133-1143.
- Meyers, L. S., Gamst, G., & Guarino, A. J. (2006). *Applied multivariate research: Design and interpretation*. Sage.
- Mugavero, M., Ostermann, J., Whetten, K., Leserman, J., Swartz, M., Stangl, D., & Thielman, N. (2006). Barriers to antiretroviral adherence: The importance of

depression, abuse, and other traumatic events. *AIDS Patient Care and STDS*, 20(6), 418-428.

Naninck, E. F., Hoeijmakers, L., Kakava- Georgiadou, N., Meesters, A., Lazic, S. E., Lucassen, P. J., & Korosi, A. (2015). Chronic early life stress alters developmental and adult neurogenesis and impairs cognitive function in mice. *Hippocampus*, 25(3), 309-328.

Navalta, C. P., Polcari, A., Webster, D. M., Boghossian, A., & Teicher, M. H. (2006). Effects of childhood sexual abuse on neuropsychological and cognitive function in college women. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 18(1), 45-53.

Nemeroff, C. (2016). Paradise lost: The neurobiological and clinical consequences of child abuse and neglect. *Neuron*, 89(5), 892-909.

Nir, T. M., Jahanshad, N., Busovaca, E., Wendelken, L., Nicolas, K., Thompson, P. M., & Valcour, V. G. (2014). Mapping white matter integrity in elderly people with HIV. *Human Brain Mapping*, 35(3), 975-992.

Norman, M. A., Moore, D. J., Taylor, M., Franklin Jr, D., Cysique, L., Ake, C., ... & HNRC Group. (2011). Demographically corrected norms for African Americans and Caucasians on the hopkins verbal learning test–revised, brief visuospatial memory test–revised, stroop color and word test, and wisconsin card sorting test 64-card version. *Journal of Clinical and Experimental Neuropsychology*, 33(7), 793-804.

- Ortega, M., Heaps, J. M., Joska, J., Vaida, F., Seedat, S., Stein, D. J., & ... Ances, B. M. (2013). HIV clades B and C are associated with reduced brain volumes. *Journal of NeuroVirology*, *19*(5), 479-487.
- Palella, F. J., Delaney, K. M., Moorman, A. C., Loveless, M. O., Fuhrer, J., Satten, G. A., . . . HIV Outpatient Study Investigators. (1998). Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *The New England Journal of Medicine*, *338*(13), 853-860.
- Palella Jr, F. J., Baker, R. K., Moorman, A. C., Chmiel, J. S., Wood, K. C., Brooks, J. T., . . . HIV Outpatient Study Investigators. (2006). Mortality in the highly active antiretroviral therapy era: Changing causes of death and disease in the HIV outpatient study. *Journal of Acquired Immune Deficiency Syndromes*, *43*(1), 27-34.
- Paul, R.H, Henry, L., Grieve, S. M., Guilmette, T. J., Niaura, R., Bryant, R., & ... Gordon, E. (2008). The relationship between early life stress and microstructural integrity of the corpus callosum in a non-clinical population. *Neuropsychiatric Disease and Treatment*, *4*(1-B), 193-201.
- Paul, R. H., Joska, J. A., Woods, C., Seedat, S., Engelbrecht, S., Hoare, J., ... & Salminen, L. E. (2014). Impact of the HIV Tat C30C31S dicysteine substitution on neuropsychological function in patients with clade C disease. *Journal of NeuroVirology*, *20*(6), 627-635.
- Paul, R. H., Phillips, S., Hoare, J., Laidlaw, D. H., Cabeen, R., Olbricht, G. R., . . . Joska, J. (2016). Neuroimaging abnormalities in clade C HIV are independent of tat genetic diversity. *Journal of NeuroVirology*, 1-10.

- Pechtel, P., & Pizzagalli, D. A. (2011). Effects of early life stress on cognitive and affective function: An integrated review of human literature. *Psychopharmacology*, *214*(1), 55-70.
- Peng, C. Y. J., Harwell, M., Liou, S. M., & Ehman, L. H. (2006). Advances in missing data methods and implications for educational research. *Real Data Analysis*, 31-78.
- Pfefferbaum, A., Rosenbloom, M. J., Rohlfing, T., Kemper, C. A., Deresinski, S., & Sullivan, E. V. (2009). Frontostriatal fiber bundle compromise in HIV infection without dementia. *AIDS*, *23*(15), 1977-1985.
- Piatt, A. L., Fields, J. A., Paolo, A. M., & Tröster, A. I. (1999). Action (verb naming) fluency as an executive function measure: Convergent and divergent evidence of validity. *Neuropsychologia*, *37*(13), 1499-1503.
- Piatt, A. L., Fields, J. A., Paolo, A. M., & Tröster, A. I. (2004). Action verbal fluency normative data for the elderly. *Brain and Language*, *89*, 580 – 583.
- Pineau, H., Marchand, A., & Guay, S. (2014). Objective neuropsychological deficits in post-traumatic stress disorder and mild traumatic brain injury: what remains beyond symptom similarity? *Behavioral Sciences*, *4*(4), 471-486.
- Poletti, S., Mazza, E., Bollettini, I., Locatelli, C., Cavallaro, R., Smeraldi, E., & Benedetti, F. (2015). Adverse childhood experiences influence white matter microstructure in patients with schizophrenia. *Psychiatry Research: Neuroimaging*, *234*(1), 35-43.
- Poletti, S., Locatelli, C., Radaelli, D., Lorenzi, C., Smeraldi, E., Colombo, C., & Benedetti, F. (2014). Effect of early stress on hippocampal gray matter is

influenced by a functional polymorphism in EAAT2 in bipolar disorder. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 51, 146-152.

Pomara, N., Crandall, D. T., Choi, S. J., Johnson, G., & Lim, K. O. (2001). White matter abnormalities in HIV-1 infection: A diffusion tensor imaging study. *Psychiatry Research: Neuroimaging*, 106(1), 15-24.

Powderly, W. G. (2002). Sorting through confusing messages: The art of HAART. *Journal of Acquired Immune Deficiency Syndromes*, 31(Suppl 1), S3-S9.

Raposa, E. B., Bower, J. E., Hammen, C. L., Najman, J. M., & Brennan, P. A. (2014). A developmental pathway from early life stress to inflammation: The role of negative health behaviors. *Psychological Science*, 25(6), 1268-1274.

Ragin, A. B., Storey, P., Cohen, B. A., Edelman, R. R., & Epstein, L. G. (2004a). Disease burden in HIV-associated cognitive impairment: A study of whole-brain imaging measures. *Neurology*, 63(12), 2293-2297.

Ragin, A. B., Storey, P., Cohen, B. A., Epstein, L. G., & Edelman, R. R. (2004b). Whole brain diffusion tensor imaging in HIV-associated cognitive impairment. *American Journal of Neuroradiology*, 25(2), 195-200.

Reitan, R.M., & Davison, L.A. (1974). *Clinical neuropsychology: Current status and applications*. Oxford, England: V.H. Winston & Sons.

Robertson, K. R., Smurzynski, M., Parsons, T. D., Wu, K., Bosch, R. J., Wu, J., & ... Ellis, R. J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *AIDS*, 21(14), 1915-1921.

- Sacktor, N., Skolasky, R. L., Seaberg, E., Munro, C., Becker, J. T., Martin, E., ... & Miller, E. (2016). Prevalence of HIV-associated neurocognitive disorders in the Multicenter AIDS Cohort Study. *Neurology*, *86*(4), 334-340.
- Saleh, A., Potter, G. G., McQuoid, D. R., Boyd, B., Turner, R., MacFall, J. R., & Taylor, W. D. (2017). Effects of early life stress on depression, cognitive performance and brain morphology. *Psychological Medicine*, *47*(1), 171.
- Sánchez, M. M., Hearn, E. F., Do, D., Rilling, J. K., & Herndon, J. G. (1998). Differential rearing affects corpus callosum size and cognitive function of rhesus monkeys. *Brain Research*, *812*(1), 38-49.
- Sanders, B., & Becker-Lausen, E. (1995). The measurement of psychological maltreatment: Early data on the child abuse and trauma scale. *Child Abuse & Neglect*, *19*(3), 315-323.
- Sanford, R., Cruz, A. L. F., Scott, S. C., Mayo, N. E., Fellows, L. K., Ances, B. M., & Collins, D. L. (2017). Regionally Specific brain volumetric and cortical thickness changes in HIV-infected patients in the HAART era. *Journal of Acquired Immune Deficiency Syndromes*, *74*(5), 563-570.
- Sasson, E., Doniger, G. M., Pasternak, O., Tarrasch, R., & Assaf, Y. (2013). White matter correlates of cognitive domains in normal aging with diffusion tensor imaging. *Frontiers in Neuroscience*, *7*(7), 32.
- Schulte, T., Müller-Oehring, E. M., Sullivan, E. V., & Pfefferbaum, A. (2012). White matter fiber compromise contributes differentially to attention and emotion processing impairment in alcoholism, HIV–infection, and their comorbidity. *Neuropsychologia*, *50*(12), 2812-2822.

- Seckfort, D. L., Paul, R., Grieve, S. M., Vandenberg, B., Bryant, R. A., Williams, L. M., & ... Gordon, E. (2008). Early life stress on brain structure and function across the lifespan: A preliminary study. *Brain Imaging and Behavior*, 2(1), 49-58.
- Shannon, C., Douse, K., McCusker, C., Feeney, L., Barrett, S., & Mulholland, C. (2009). The association between childhood trauma and memory functioning in schizophrenia. *Schizophrenia Bulletin*, sbp096.
- Simioni, S., Cavassini, M., Annoni, J. M., Abraham, A. R., Bourquin, I., Schiffer, V., ... & Du Pasquier, R. A. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *AIDS*, 24(9), 1243-1250.
- Simoni, J. M., & Ng, M. T. (2000). Trauma, coping and depression among women with HIV/AIDS in New York City. *AIDS Care*, 12(5), 567-580.
- Smith, S. M. (2002). Fast robust automated brain extraction. *Human Brain Mapping*, 17(3), 143-155.
- Smith, S. M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T. E., Mackay, C. E., . . . Behrens, T. E. J. (2006). Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. *Neuroimage*, 31(4), 1487-1505.
- Smith, S. M., & Nichols, T. E. (2009). Threshold-free cluster enhancement: Addressing problems of smoothing, threshold dependence and localisation in cluster inference. *Neuroimage*, 44(1).
- Spies, G., Afifi, T. O., Archibald, S. L., Fennema-Notestine, C., Sareen, J., & Seedat, S. (2012). Mental health outcomes in HIV and childhood maltreatment: A systematic review. *Systematic Reviews*, 1(1), 30-30.

- Spies, G., Ahmed-Leitao, F., Fennema-Notestine, C., Cherner, M., & Seedat, S. (2016). Effects of HIV and childhood trauma on brain morphometry and neurocognitive function. *Journal of NeuroVirology*, 22(2), 149-158.
- Spies, G., Fennema-Notestine, C., Cherner, M., & Seedat, S. (2017). Changes in cognitive function in women with HIV infection and early life stress. *Aids Care- Psychological and Socio-Medical Aspects of AIDS/HIV*, 29(1), 14-23.
- Stein, M. B., Hanna, C., Vaerum, V., & Koverola, C. (1999). Memory functioning in adult women traumatized by childhood sexual abuse. *Journal of Traumatic Stress*, 12(3), 527-534.
- Stein, M. B., Koverola, C., Hanna, C., Torchia, M. G., & McClarty, B. (1997). Hippocampal volume in women victimized by childhood sexual abuse. *Psychological Medicine*, 27(4), 951-959.
- Stubbe-Dräger, B., Deppe, M., Mohammadi, S., Keller, S. S., Kugel, H., Gregor, N., & ... Husstedt, I. W. (2012). Early microstructural white matter changes in patients with HIV: A diffusion tensor imaging study. *BMC Neurology*, 12(1), 23.
- Song, S., Sun, S., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *Neuroimage*, 17(3), 1429-1436.
- Spudich, S. (2013). HIV and neurocognitive dysfunction. *Current HIV/AIDS Reports*, 10(3), 235-243.
- Strain, J. F., Didehbani, N., Spence, J., Conover, H., Bartz, E. K., Mansinghani, S., & ... Womack, K. B. (2017). White matter changes and confrontation naming in retired

aging National Football League athletes. *Journal of Neurotrauma*, 34(2), 372-379.

Su, T., Caan, M. W., Wit, F. W., Schouten, J., Geurtsen, G. J., Cole, J. H., ... & Reiss, P. (2016). White matter structure alterations in HIV-1-infected men with sustained suppression of viraemia on treatment. *AIDS*, 30(2), 311-322.

Sullivan, E. V., Adalsteinsson, E., & Pfefferbaum, A. (2006). Selective age-related degradation of anterior callosal fiber bundles quantified in vivo with fiber tracking. *Cerebral Cortex*, 16(7), 1030-1039.

Tabachnick, B. G., Fidell, L. S., & Osterlind, S. J. (2001). Using multivariate statistics.

Tate, D. F., Conley, J., Paul, R. H., Coop, K., Zhang, S., Zhou, W., & ... Tashima, K. (2010). Quantitative diffusion tensor imaging tractography metrics are associated with cognitive performance among HIV-infected patients. *Brain Imaging and Behavior*, 4(1), 68-79.

Tavakoli, H. (2012). *A dictionary of research methodology and statistics in applied linguistics*. Rahnama press.

Teicher, M. H., Andersen, S. L., Polcari, A., Anderson, C. M., Navalta, C. P., & Kim, D. M. (2003). The neurobiological consequences of early stress and childhood maltreatment. *Neuroscience & Biobehavioral Reviews*, 27(1), 33-44.

Thurnher, M., Stadler, A., Rieger, A., Schmid, B., Sundgren, P., & Castillo, M. (2005). Diffusion-tensor MR imaging of the brain in human immunodeficiency virus-positive patients. *American Journal of Neuroradiology*, 26(9), 2275-2281.

- Underwood, J., Cole, J. H., Caan, M., De Francesco, D., Leech, R., van Zoest, R. A., ... & Prins, M. (2017). Grey and white matter abnormalities in treated HIV-disease and their relationship to cognitive function. *Clinical Infectious Diseases*.
- Valcour, V., Chalermchai, T., Sailasuta, N., Marovich, M., Lerdlum, S., Suttichom, D., ... & van Griensven, F. (2012). Central nervous system viral invasion and inflammation during acute HIV infection. *Journal of Infectious Diseases*, 206(2), 275-282.
- Valcour, V., Shikuma, C., Shiramizu, B., Watters, M., Poff, P., Selnes, O., ... & Sacktor, N. (2004). Higher frequency of dementia in older HIV-1 individuals The Hawaii Aging with HIV-1 Cohort. *Neurology*, 63(5), 822-827.
- Valcour, V., Yee, P., Williams, A. E., Shiramizu, B., Watters, M., Selnes, O., ... & Sacktor, N. (2006). Lowest ever CD4 lymphocyte count (CD4 nadir) as a predictor of current cognitive and neurological status in human immunodeficiency virus type 1 infection—The Hawaii Aging with HIV Cohort. *Journal of NeuroVirology*, 12(5), 387-391.
- van der Vegt, E. M., van der Ende, J., Kirschbaum, C., Verhulst, F. C., & Tiemeier, H. (2009). Early neglect and abuse predict diurnal cortisol patterns in adults: A study of international adoptees. *Psychoneuroendocrinology*, 34(5), 660-669.
- van Harmelen, A. L., van Tol, M. J., van der Wee, N. J., Veltman, D. J., Aleman, A., Spinhoven, P., ... & Elzinga, B. M. (2010). Reduced medial prefrontal cortex volume in adults reporting childhood emotional maltreatment. *Biological Psychiatry*, 68(9), 832-838.

- Villar-Loubet, O. M., Illa, L., Echenique, M., Cook, R., Messick, B., Duthely, L. M., ... & Potter, J. (2014). Prenatal and mental health care among trauma-exposed, HIV-infected, pregnant women in the United States. *Journal of the Association of Nurses in AIDS Care*, 25(1), S50-S61.
- Walton, G., Co, S. J., Milloy, M., Qi, J., Kerr, T., & Wood, E. (2011). High prevalence of childhood emotional, physical and sexual trauma among a Canadian cohort of HIV-seropositive illicit drug users. *AIDS Care*, 23(6), 714-721.
- Wang, B., Liu, Z., Liu, J., Tang, Z., Li, H., & Tian, J. (2015). Gray and white matter alterations in early HIV- infected patients: Combined voxel- based morphometry and tract- based spatial statistics. *Journal of Magnetic Resonance Imaging*. 43(6), 1474-1483.
- Wang, Z., Neylan, T. C., Mueller, S. G., Lenoci, M., Truran, D., Marmar, C. R., & ... Schuff, N. (2010). Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. *Archives of General Psychiatry*, 67(3), 296-303.
- Wechsler, D. (1997). *WAIS-III: Wechsler adult intelligence scale*. San Antonio, TX: Psychological Corporation.
- Whetten, K., Leserman, J., Lowe, K., Stangl, D., Thielman, N., Swartz, M., & ... Moore, M. (2006). Prevalence of childhood sexual abuse and physical trauma in an HIV-positive sample from the deep south. *American Journal of Public Health*, 96(6), 1028-1030.
- Whitford, T. J., Kubicki, M., & Shenton, M. E. (2011). Diffusion tensor imaging, structural connectivity, and schizophrenia. *Schizophrenia Research and Treatment*, 2011.

- World Health Organization. (2017). *Global Health Observatory (GHO) data*. Retrieved from <http://www.who.int/gho/hiv/en/>
- Winkler, A. M., Ridgway, G. R., Webster, M. A., Smith, S. M., & Nichols, T. E. (2014). Permutation inference for the general linear model. *Neuroimage*, (92), 381-397.
- Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychology Review*, 19(2), 152-168.
- Woods, S. P., Scott, J. C., Dawson, M. S., Morgan, E. E., Carey, C. L., Heaton, R. K., & Grant, I. (2005a). Construct validity of Hopkins Verbal Learning Test--Revised component process measures in an HIV-1 sample. *Archives of Clinical Neuropsychology*, 20(8), 1061-1071.
- Woods, S. P., Scott, J. C., Sires, D. A., Grant, I., Heaton, R. K., Tröster, A. I., & HIV Neurobehavioral Research Center (HNRC) Group. (2005b). Action (verb) fluency: Test-retest reliability, normative standards, and construct validity. *Journal of the International Neuropsychological Society*, 11(04), 408-415.
- Wright, P. W., Heaps, J. M., Shimony, J. S., Thomas, J. B., & Ances, B. M. (2012). The effects of HIV and combination antiretroviral therapy on white matter integrity. *AIDS*, 26(12), 1501-1508.
- Wu, Y., Storey, P., Cohen, B. A., Epstein, L. G., Edelman, R. R., & Ragin, A. B. (2006). Diffusion alterations in corpus callosum of patients with HIV. *American Journal of Neuroradiology*, 27(3), 656-660.
- Zhu, T., Zhong, J., Hu, R., Tivarus, M., Ekholm, S., Harezlak, J., ... & Schifitto, G. (2013). Patterns of white matter injury in HIV infection after partial immune

reconstitution: a DTI tract-based spatial statistics study. *Journal of NeuroVirology*, 19(1), 10-23.

Table 1

Demographic Characteristics for Primary Aims

Variable	HIV+/high ELS n = 91	HIV+/low ELS n = 39	HIV-/high ELS n = 45	HIV-/low ELS n = 31
Mean age (years) (SD)*	50.71 (13.26)	52.46 (12.52)	33.73 (16.01)	38.16 (15.90)
Mean education (years) (SD)	13.30 (2.77)	14.00 (2.92)	13.98 (2.06)	13.42 (1.82)
Ethnic composition				
% Caucasian	38%	33%	47%	42%
% African American	59%	64%	51%	52%
% American Indian	1%	0%	0%	0%
% Asian	0%	0%	0%	6%
% Multiracial	2%	3%	2%	0%
% Male*	79%	82%	49%	45%
Mean BDI-II score (SD)*	9.15 (7.34)	8.18 (7.37)	6.60 (5.63)	4.90 (6.59)
Mean number of ELS events (SD)*	5.47 (2.41)	1.03 (0.90)	5.29 (2.14)	0.90 (0.60)
Mean duration of infection (years) (SD)	16.05 (9.16)	13.69 (7.86)	-	-
% on HAART	100%	100%	-	-
Duration of HAART (years) (SD)	12.80 (7.69)	11.41 (7.44)		
Years between diagnosis and HAART (SD)	2.12 (2.41)	1.44 (2.71)		
Mean nadir CD4 (cells/μl) (SD)	179.22 (175.31)	183.15 (166.86)	-	-
Mean current CD4 (cells/μl) (SD)	620.20 (311.05)	570.00 (262.20)	-	-
Mean viral load (SD)	1.55 (0.70)	1.56 (0.87)	-	-
% undetectable viral load (< 20 copies/ml)	81%	82%	-	-
% HAART treatment regimen				
NRTI + NNRTI	34%	33%		
NRTI + PI	12%	23%		
NRTI + INSTI	27%	26%		
Other HAART	27%	18%		
% Substance Use (last 6 months)				
Alcohol	68%	68%	75%	64%
Opiates	2%	0%	0%	0%
Crack/Cocaine	10%	7%	3%	4%
Marijuana	33%	38%	32%	25%
Amphetamines	1%	1%	0%	0%
% Cognitive Impairment	31%	40%	29%	16%

Note. ^a Viral load log₁₀ transformed; *Significant difference between groups $p < 0.05$; BDI-II = Beck Depression Inventory-II; NRTI = nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor; INSTI = integrase strand transfer inhibitors; HAART = highly active antiretroviral therapy

Table 2

DTI Metrics in HIV/ELS Groups

	HIV+/high ELS	HIV+/low ELS	HIV-/high ELS	HIV-/low ELS
DTI Metric	M (SD)	M (SD)	M (SD)	M (SD)
Fractional Anisotropy				
Uncinate Fasciculus	0.54 (0.04)	0.55 (0.03)	0.55 (0.03)	0.55 (0.04)
Cingulate gyrus segment of cingulum	0.60 (0.03)	0.60 (0.03)	0.60 (0.03)	0.61 (0.03)
Hippocampal segment of cingulum	0.51 (0.06)	0.52 (0.05)	0.50 (0.06)	0.50 (0.06)
Corpus Callosum	0.77 (0.04)	0.77 (0.03)	0.79 (0.04)	0.78 (0.02)
Axial Diffusivity (10⁻²)				
Uncinate Fasciculus	0.12 (0.00)	0.12 (0.00)	0.12 (0.00)	0.12 (0.00)
Cingulate gyrus segment of cingulum	0.11 (0.00)	0.12 (0.00)	0.12 (0.00)	0.12 (0.00)
Hippocampal segment of cingulum	0.09 (0.00)	0.09 (0.00)	0.09 (0.00)	0.10 (0.00)
Corpus Callosum	0.14 (0.00)	0.14 (0.00)	0.14 (0.00)	0.14 (0.00)
Radial Diffusivity (10⁻³)				
Uncinate Fasciculus	0.46 (0.00)	0.46 (0.00)	0.45 (0.00)	0.45 (0.00)
Cingulate gyrus segment of cingulum	0.34 (0.00)	0.34 (0.00)	0.34 (0.00)	0.33 (0.00)
Hippocampal segment of cingulum	0.42 (0.00)	0.41 (0.00)	0.43 (0.00)	0.43 (0.00)
Corpus Callosum	0.28 (00.00)	0.28 (0.00)	0.26 (0.00)	0.26 (0.00)

Note. *Significant difference between groups $p < 0.05$ following FDR correction; DTI = diffusion tensor imaging

Table 3

Brain Volumes in HIV/ELS Groups

Brain Region of Interest cm ³	HIV+/high ELS	HIV+/low ELS	HIV-/high ELS	HIV-/low ELS
	M (SD)	M (SD)	M (SD)	M (SD)
Anterior cingulate cortex	8.40 (1.38)	8.11 (1.27)	8.81 (1.65)	8.43 (1.26)
Hippocampus*	7.84 (1.06)	7.59 (0.85)	8.23 (0.86)	8.35 (0.73)
Amygdala*	3.27 (0.49)	3.21 (0.38)	3.50 (0.46)	3.51 (0.31)
Caudate	7.01 (0.97)	6.87 (0.93)	7.34 (1.04)	7.27 (1.22)
Putamen*	10.51 (1.35)	10.26 (1.07)	11.73 (1.44)	11.48 (1.33)
Corpus callosum*	3.02 (0.53)	2.87 (0.46)	3.17 (0.44)	3.21 (0.50)

Note. *Significant difference between groups $p < 0.05$ following FDR correction

Table 4

Cognitive Test Scores in HIV/ELS Groups

Cognitive Test	HIV+/high ELS M (SD)	HIV+/low ELS M (SD)	HIV-/high ELS M (SD)	HIV-/low ELS M (SD)
Psychomotor/Processing Speed				
Trails A [^]	31.64 (10.38)	33.86 (11.82)	29.66 (9.97)	26.09 (9.03)
Grooved Pegboard- dominant hand [^]	76.88 (16.59)	77.20 (9.15)	67.74 (12.53)	67.05 (11.18)
Grooved Pegboard- nondominant hand [^]	84.91 (17.79)	90.69 (13.31)	80.55 (15.86)	77.76 (12.96)
Digit Symbol Substitution Test	64.99 (15.66)	65.23 (18.30)	76.12 (14.97)	77.65 (17.46)
Executive Function*				
Trails B [^]	82.32 (32.02)	85.04 (33.23)	72.42 (30.88)	61.51 (16.44)
Verb Fluency*	12.96 (5.77)	12.57 (6.32)	17.51 (7.67)	15.71 (6.69)
LNS*	8.53 (3.00)	9.30 (2.81)	10.39 (2.55)	11.04 (2.47)
Trial 3 of the CWIT* [^]	67.67 (17.21)	65.29 (17.86)	52.09 (14.06)	49.94 (12.71)
Learning				
HVLT-R Learning	21.91 (5.60)	21.74 (6.13)	24.09 (4.57)	24.00 (4.85)

Note. *Significant difference between groups $p < 0.05$ following FDR correction; [^] indicates lower score equals better performance; LNS = letter number sequencing; HVLT-R = Hopkins Verbal Learning Test-Revised

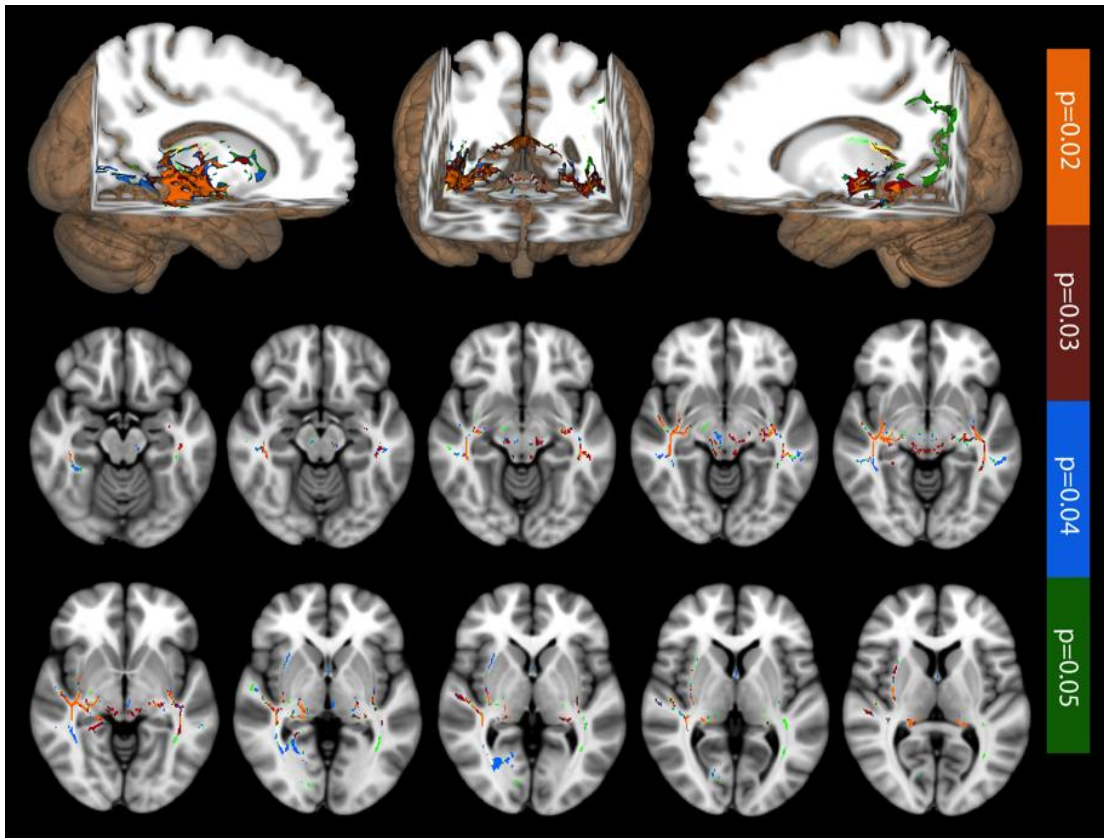


Figure 1. TBSS voxel-wise comparison of fractional anisotropy (FA) differences between HIV+ individuals and HIV- individuals on diffusion tensor imaging. Orange indicates voxels in which FA is lower in HIV+ individuals than HIV- individuals ($p < 0.02$, corrected). Red indicates voxels in which FA is lower in HIV+ individuals than HIV- individuals ($p < 0.03$, corrected). Blue indicates voxels in which FA is lower in HIV+ individuals than HIV- individuals ($p < 0.04$, corrected). Green indicates voxels in which FA is lower in HIV+ individuals than HIV- individuals ($p < 0.05$, corrected). Axial images are in radiologic orientation with the results thickened for better visibility using the tract-based spatial statistics “fill” script.

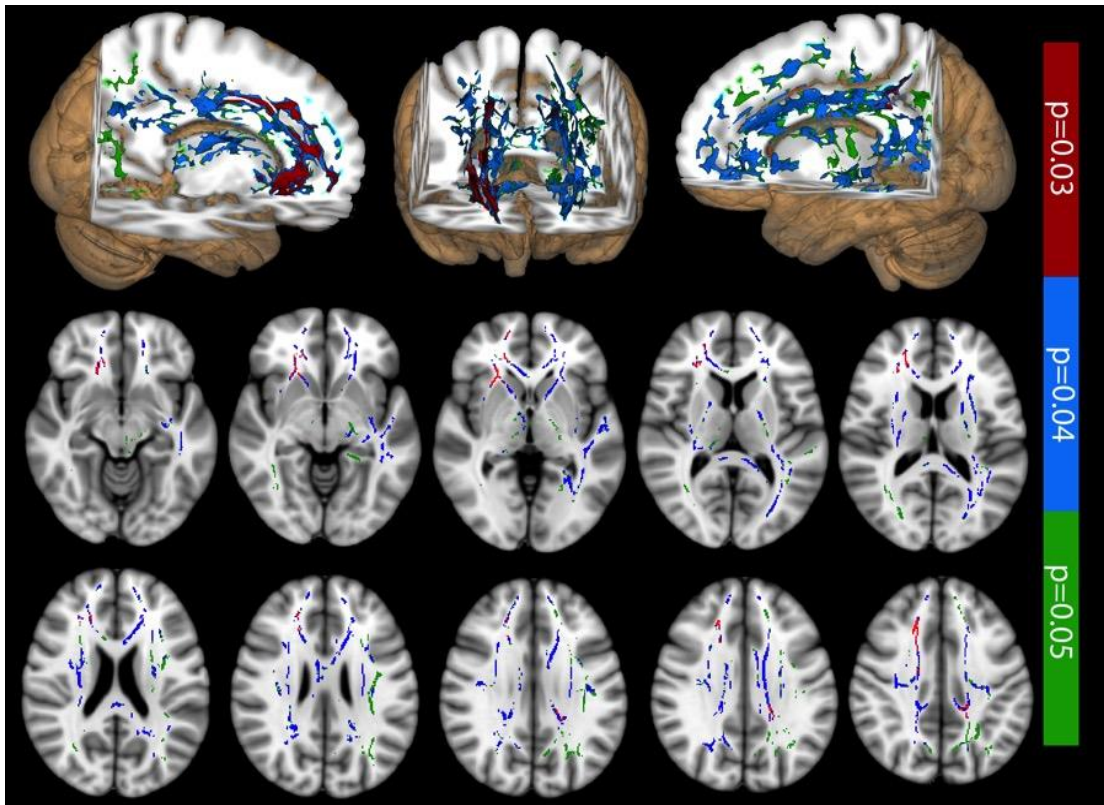


Figure 2. TBSS voxel-wise comparison of fractional anisotropy (FA) differences between individuals with high ELS and individuals with low ELS on diffusion tensor imaging. Orange indicates voxels in which FA is lower in high ELS than low ELS ($p < 0.02$, corrected). Red indicates voxels in which FA is lower in high ELS than low ELS ($p < 0.03$, corrected). Blue indicates voxels in which FA is lower in high ELS than low ELS ($p < 0.04$, corrected). Green indicates voxels in which FA is lower in high ELS than low ELS ($p < 0.05$, corrected). Axial images are in radiologic orientation with the results thickened for better visibility using the tract-based spatial statistics “fill” script.

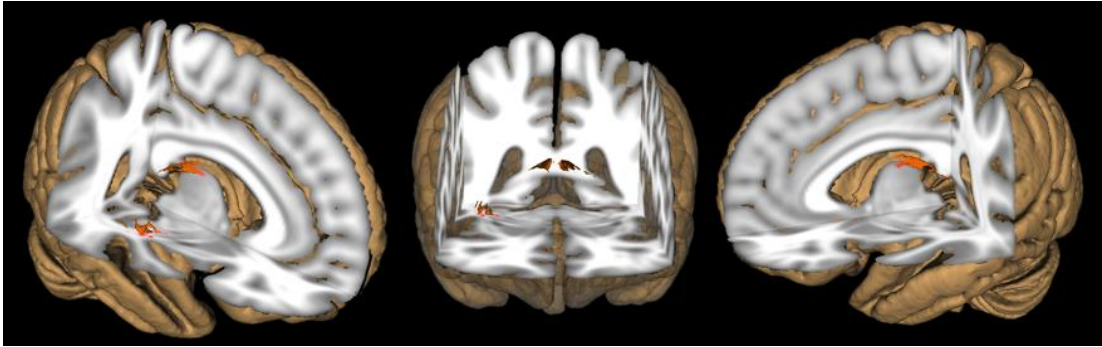


Figure 3. TBSS voxel-wise comparison of radial diffusivity (RD) differences between HIV+ individuals and HIV- individuals on diffusion tensor imaging. Orange indicates voxels in which RD is higher in HIV+ individuals than HIV- individuals ($p < 0.05$, corrected).

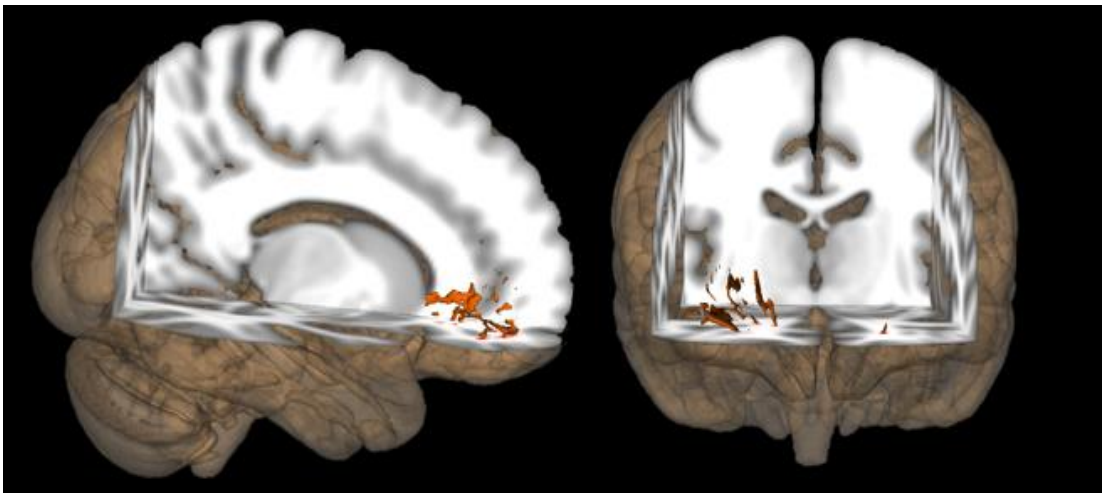


Figure 4. TBSS voxel-wise comparison of radial diffusivity (RD) differences between individuals with high ELS and low ELS on diffusion tensor imaging. Orange indicates voxels in which RD is higher in individuals with high ELS than individuals with low ELS ($p < 0.05$, corrected).

Supplement

Supplemental Table 1

Correlations Between Brain volumes and Cognition (Spies et al., 2016)

Cognitive Domain	Brain Volume
Motor Skills	Anterior Cingulate Cortex
Processing Speed	Anterior Cingulate Cortex Corpus Callosum Amygdala Caudate
Learning	Hippocampus
Verbal Fluency	Hippocampus Corpus Callosum
Attention/Working Memory	Corpus Callosum
Abstraction/Executive Function	Amygdala Caudate

Supplemental Table 2

Neuropsychological Test Battery and Normative Data

Neuropsychological domain and tests	Normative data sources
Learning	
Hopkins Verbal Learning Test- Revised (Total Immediate Recall)	Benedict, Schretlen, Groninger & Brandt (1998) ¹ ; Friedman et al., 2002 ^{1,2,3} ; Norman et al., 2011 ^{2,3}
Psychomotor/Processing Speed	
WAIS-III Digit Symbol	Weschler (1997) ¹
Trail Making Test (Part A)	Heaton, Miller, Taylor & Grant (2004) ^{1,2,3,4} ; Lucas et al., 2005 ^{1,2,4}
Grooved Pegboard (dominant hand)	Heaton, Miller, Taylor & Grant (2004) ^{1,2,3,4}
Grooved Pegboard (non-dominant hand)	Heaton, Miller, Taylor & Grant (2004) ^{1,2,3,4}
Executive Function	
WAIS-III Letter Number Sequencing	Weschler (1997) ¹
Trial 3 of the Color Word Interference Task	Delis, Kaplan, & Kramer (2001) ¹
Trail Making Test (Part B)	Heaton, Miller, Taylor & Grant (2004) ^{1,2,3,4} ; Lucas et al., 2005 ^{1,2,4}
Verb Fluency	Piatt et al., 2004 ^{1,2} ; Woods et al., 2005b ²

Note. WAIS-III = Wechsler Adult Intelligence Scale-III; Normative data indicated by superscript number- 1 = age, 2 =education, 3= gender, 4= ethnicity

Supplemental Table 3

Whole-Brain DTI Skeletal Values in HIV/ELS Groups

DTI Metric	HIV+/high ELS	HIV+/low ELS	HIV-/high ELS	HIV-/low ELS
	M (SD)	M (SD)	M (SD)	M (SD)
Fractional Anisotropy	0.49 (0.02)	0.50 (0.03)	0.50 (0.22)	0.51 (.02)
Axial Diffusivity (10^{-2})	0.11 (0.00)	0.11 (0.00)	0.11 (0.00)	0.11 (0.00)
Radial Diffusivity (10^{-3})	0.49 (0.00)	0.48 (0.00)	0.47 (0.00)	0.48 (0.00)