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Effects of HIV and childhood trauma on brain morphometry and neurocognitive function

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Abstract A wide spectrum of neurocognitive deficits characterises HIV infection in adults. HIV infection is additionally associated with morphological brain abnormalities affecting neural substrates that subserve neurocognitive function. Early life stress (ELS) also has a direct influence on brain morphology. However, the combined impact of ELS and HIV on brain structure and neurocognitive function has not been examined in an all-female sample with advanced HIV disease. The present study examined the effects of HIV and childhood trauma on brain morphometry and neurocognitive function. Structural data were acquired using a 3T Magnetom MRI scanner, and a battery of neurocognitive tests was administered to 124 women: HIV-positive with ELS (n=32), HIV-positive without ELS (n=30), HIV-negative with ELS (n=31) and HIV-negative without ELS (n=31). Results revealed significant group volumetric differences for right anterior cingulate cortex (ACC), bilateral hippocampi, corpus callosum, left and right caudate and left and right putamen. Mean regional volumes were lowest in HIV-positive women with ELS compared to all other groups. Although causality cannot be inferred, findings also suggest that alterations in the left frontal lobe, right ACC, left hippocampus, corpus callosum, left and right amygdala and left caudate may be associated with poorer neurocognitive performance in the domains of processing speed, attention/working memory, abstraction/executive functions, motor skills, learning and language/fluency with these effects more pronounced in women living with both HIV and childhood trauma. This study highlights the potential contributory role of childhood trauma to brain alterations and neurocognitive decline in HIV-infected individuals.

Keywords HIV · Childhood trauma · MRI · Brain volumetrics · FreeSurfer · Neurocognition

Introduction

In 2014, an estimated 5.51 million South Africans were infected with human immunodeficiency virus (HIV), and for women aged 15–49, an estimated 18.5 % of the population was HIV-positive (Statistics South Africa 2014). Among South African women, high rates of intimate partner violence, rape and childhood abuse have been reported (Andersson et al. 2008; Jewkes et al. 2001, 2002; Kalichman and Simbayi 2004). Many women infected with HIV in adulthood also have developmental trajectories characterised by trauma. Such trauma has been associated with poor neurocognitive functioning and other neurologic and psychiatric sequelae (Malan-Muller et al. 2013; Spies et al. 2012a, b; Troeman et al. 2011). The brain and behavioural changes that attend early life trauma may, in this vulnerable population, result in additional complications related to the course of HIV disease.

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However, the impact that early life stress (ELS) may have on the presentation and neuropathology of HIV has received very little attention.

HIV penetrates the blood-brain barrier early in the course of infection and can be highly neurovirulent (Valcour et al. 2012), infecting nerve cells and resulting in neuroinflammation and neuronal death (Kumar et al. 2009). HIV-infected individuals commonly have neurocognitive deficits characterised as HIV-associated neurocognitive disorders (HANDs) (Antinori et al. 2007). In addition, morphological brain abnormalities are common (Holt et al. 2012; Letendre et al. 2009), and these abnormalities may be similar across various genetic clades of the virus (Ortega et al. 2013). Studies have reported volumetric, functional and metabolite abnormalities in HIV-infected individuals most commonly within frontal-striatal brain regions (Ances et al. 2006; Aylward et al. 1993; Becker et al. 2011; Cohen et al. 2010b; Jernigan et al. 1993; Paul et al. 2002; Towgood et al. 2012), and these abnormalities have been linked to poor cognitive performance (Castelo et al. 2006; Cohen et al. 2010a; Harezlak et al. 2011; Melrose et al. 2008; Moore et al. 2006; Paul et al. 2008b). Risk for significant brain involvement, as manifested by both neuroimaging abnormalities and neurocognitive impairments, is higher with more advanced disease stage and with greater immunocompromise (e.g. lower nadir CD4) (Centers for Disease Control and Prevention 1993; Ellis et al. 2011; Heaton et al. 1995). Even with effective antiretroviral therapy (ART), individuals who are HIV-infected continue to demonstrate ongoing aberrations in white and grey matter, as demonstrated by recent neuroimaging studies (Becker et al. 2011, 2012; Cardenas et al. 2009; Cohen et al. 2010a, b; Jernigan et al. 2011). Recent evidence further suggests that increases in brain white matter and subcortical grey matter abnormalities are linked to CD4 recovery among infected individuals (Fennema-Notestine et al. 2013). The continued presence of brain abnormalities and neurocognitive impairments, despite improvements in treatment, suggests ongoing low-grade infection and/or chronic inflammation.

A growing body of evidence indicates that ELS can have pathological brain effects (Andersen et al. 2008; Choi et al. 2009; Cohen et al. 2006; Mehta et al. 2009; Paul et al. 2008a; Seckfort et al. 2008; Stein et al. 1997; Teicher et al. 2004; Tottenham et al. 2010) in otherwise healthy individuals. In clinical samples (e.g. PTSD and major depression), studies of ELS have similarly identified stress-related structural, functional and metabolite alterations in individuals who have suffered adverse childhood events, such as abuse (Bremner et al. 1997, 2003; De Bellis et al. 2000; Vythilingam et al. 2002), as well as events in adulthood (e.g. intimate partner violence (IPV)) (Fennema-Notestine et al. 2002; Seedat et al. 2005). These alterations include structural abnormalities in the amygdala, hippocampus, corpus callosum, anterior cingulate cortex and caudate nuclei in individuals with ELS and in supratentorial cranial vaults in individuals with IPV. Studies in HIV-infected individuals have reported high rates of childhood emotional, physical and sexual abuse (Allers and Benjack 1991; Cohen et al. 2000; Walton et al. 2011), and ELS may increase the risk for HAND or compound HIV-related neural abnormalities.

To the best of our knowledge, only a single cross-sectional study has directly examined the combined impact of HIV infection and ELS on brain volumes and associated neurocognitive functioning. Clark et al. studied four groups of individuals with and without HIV infection and/or trauma histories in the USA, where clade B HIV predominates and the majority of individuals are on antiretroviral treatment (Clark et al. 2012). Their findings supported an interaction between HIV status and ELS severity, such that larger amygdala volumes were evident in HIV-infected individuals with high levels of ELS. These abnormalities were associated with neurocognitive dysfunction (Clark et al. 2012). The aforementioned study examined relatively complex groups that differed with respect to education, current stress, depression, lifetime cocaine use and HCV status, although these variables did not appear to account for the interaction of neurocognitive and neural findings.

It is against this background that the present study investigated the combined effects of HIV infection and childhood trauma on brain structure and neurocognitive performance in an all-female cohort infected with clade C HIV, less than half of whom are on treatment. Our hypothesis was twofold: firstly that women with the 'double hit' of HIV infection and childhood trauma would have significantly altered brain volumes in regions typically impacted by HIV and ELS (caudate, putamen, hippocampus, amygdala, corpus callosum and anterior cingulate) compared to HIV-positive women without childhood trauma. Secondly, we hypothesised that alterations in brain volumes in these regions in dually affected women would be associated with poorer neurocognitive performance.

Methods

Participants

A total of 124 women tested for HIV status were included: 62 were HIV-positive, 32 with a history of childhood trauma and 30 without, and 62 were HIV-negative, 31 with a history of childhood trauma and 31 without.

Eligibility criteria included willingness and ability to provide written informed consent, ability to read and write in either English, Afrikaans (a West Germanic language spoken natively in South Africa) or isiXhosa (one of the indigenous African languages spoken natively in South Africa) at fifth grade level, between 18 and 65 years of age and medically

well enough to undergo neuropsychological testing and MRI scanning. Exclusions were MRI contraindications such as pregnancy or metal in the body, a current or past history of schizophrenia, bipolar disorder or other psychotic disorders, history of substance abuse or dependence, significant previous head injury, demonstrated cognitive impairment on the HIV Dementia Scale, current seizure disorders of any cause, history of CNS infections or neoplasms, hepatitis C-positive status and current use (within the past month) of any psychotropic medication (including antidepressants).

Procedure

The study was approved by the ethics committee of Stellenbosch University, Cape Town, South Africa. All women included in the present study were tested for HIV status at their local health care facility, with HIV status confirmed by means of ELISA. Sixty two (44.6 %) women were HIV-positive. Participants were recruited through community health care facilities (VCT sites and HIV units) in and around the Cape metropole of South Africa from 2008 to 2015 by a researcher or with the help of doctors and adherence counsellors. Recruitment procedures did not differ across groups. All participants who consented were screened for eligibility and childhood trauma exposure either in person at their clinic or telephonically. Those who met initial screening criteria subsequently underwent neuromedical, neuropsychiatric, neurocognitive and neuroimaging assessments. Participants were reimbursed for travel costs to and from assessments.

Measures

Age, gender, marital status, ethnicity, years of education and employment status were captured. A comprehensive history was obtained from, and a general physical examination conducted in, all patients. Virologic markers of disease progression (CD4 lymphocyte count and viral loads) were obtained from blood samples.

The Childhood Trauma Questionnaire Short Form (CTQ-SF) was used to retrospectively elucidate trauma exposure and to categorise HIV-positive and HIV-negative women into trauma (score of 41 or higher on the CTQ indicating moderate to extreme trauma) and non-trauma exposure groups (score of 25–40 on the CTQ). The CTQ-SF is a 28-item self-report inventory that provides valid screening for histories of abuse and neglect (up until the age of 18). It assesses five types of maltreatment including, emotional, physical and sexual abuse and emotional and physical neglect. Scores range from 25 to 125, with higher scores indicating higher levels of trauma exposure during childhood (Bernstein et al. 2003). The Cronbach alpha for the CTQ was excellent (α=0.83).

Neurocognitive function was measured with 10 tests that have been used commonly in HIV research and cover seven ability domains (learning, delayed recall, processing speed, attention/working memory, executive function, verbal fluency, motor ability) (Heaton et al. 2010). Test instructions and stimuli were adapted as necessary to fit the cultural context of South Africa and translated into Afrikaans and isiXhosa using standard test adaptation techniques. Tests were administered in English, Afrikaans or isiXhosa according to the participants' self report of best language. We have previously reported group differences using this test battery (Spies et al. 2012a).

Neuroimaging data acquisition and analysis

Data were acquired using a MAGETOM Siemens Allegra syngo MR 3 Tesla scanner, with a four channel head coil. The following imaging parameters were used: TR= 2530 ms, TE=1.53 ms, TI=1100 ms, flip angle=7°, voxel size=1.3×1.0×1.3 mm, field of view=256 mm. Region-specific grey matter volumetric measurements were acquired through FreeSurfer software which is publicly available and includes probabilistic volumetric segmentation for white matter and subcortical regions and cortical surface reconstruction and parcellation for neocortical measures (Dale et al. 1999; Desikan et al. 2006; Fischl et al. 1999, 2002, 2004; Fischl and Dale 2000). The software was used in a completely automated fashion, and quality control was implemented throughout the process. The processing pipeline is computationally intensive, and as such, we utilised custom batching scripts on the Centre for High Performance Computing (CHPC) in Cape Town. All data were analysed using SPSS for Windows (version 22) and Statistica (version 12). Descriptive statistics were computed for all demographic and clinical information. We used analysis of variance (ANOVA) to assess group differences in estimated intracranial vault, age, education and brain volumes. Estimated intracranial vault was added as a covariate to control for individual differences in head size. Analysis of covariance (ANCOVA) using age and estimated intracranial vault as covariates was subsequently undertaken. Pearson's correlations assessed for associations between brain volumes and neurocognitive function as well as for associations between estimated intracranial vault and trauma subtypes on the CTQ. Homogeneity of slopes ANCOVA was conducted with regional brain volumes as dependent variables and group and neurocognitive function as independent variables. The interaction variable (group by neurocognitive outcomes) tested the relationships (slopes) between brain volumes and neurocognitive outcomes across the groups. Estimated intracranial vault, age and education were controlled for as covariates in the models. The significance level was two-sided and set at 0.05 respectively. Post hoc tests (Fisher's LSD and Bonferroni) were conducted to correct for multiple comparisons.

Results

Demographic characteristics

The mean age of participants was 30.3 years (minimum of 18 years, maximum of 50 years). The mean level of education was 10.3 years (minimum of 5 years, maximum of 14 years). The groups significantly differed in age and education, with HIV-negative participants younger and more educated than HIV-positive counterparts. The majority of the women were Black (86.3 %), Xhosa speaking (85.6 %) and right-handed (84.2 %). Further demographic details are presented in Table 1.

Clinical characteristics

Of the HIV-positive women, 30 (48.4 %) reported being on antiretroviral treatment (ART). The mean CD4 lymphocyte count was 431.20 (minimum of 25 and a maximum of 1529). The mean viral load was 116,172.08, ranging from lower than the detectable limit to 3,200,000 copies/ml. There were no significant group differences with respect to clinical variables such as CD4 lymphocyte count and viral load.

Childhood trauma

Sixty-one participants reported no childhood trauma. Among the HIV-infected women (n=62), a total of 32 reported histories of childhood trauma, one in the low to moderate range (41–55), 11 (17.7 %) in the moderate to severe range (56–72) and 20 (32.3 %) in the severe to extreme range (73–125). Among the HIV-uninfected women (n=62), a total of 31 reported histories of childhood trauma, 20 (32.3 %) in the mild to moderate range (41–55), 7 (11.3 %) in the moderate to severe range (56–72) and 4 (6.45 %) in the severe to extreme range (73–125). The overall mean score on the CTQ was 49.34 with a minimum of 25 and a maximum of 116. The most commonly reported childhood trauma type was emotional abuse with a mean of 11.55, followed by emotional neglect (M=11.34), physical neglect (M=9.76), physical abuse (M=9.30) and lastly sexual abuse (M=7.38). See Table 4. Pearson's correlation assessed the association between intracranial vault (ICV) volume and CTQ subscale scores. ICV was significantly associated with childhood physical neglect (r=0.195, p=0.030).

Regional volumetric differences between groups

Brain volumes of the following regions were significantly different among the four groups as revealed by ANCOVA, using age and intracranial vault as covariates: right ACC (p<0.05), bilateral hippocampi, corpus callosum, left and right caudate and left and right putamen (p<0.01). Mean brain volume was significantly smaller in HIV-positive women with childhood trauma, compared to the other three groups, for all the above-mentioned regions. For the left hippocampus, mean brain volume was smallest in HIV-positive women with childhood trauma, followed by HIV-negative women with childhood trauma. Mean brain volume of the left amygdala and right amygdala was smallest in the dually affected group although group differences did not reach statistical significance (p=0.05). See Table 2.

Associations between regional brain volumes and neurocognition

There were no significant correlations between CD4 lymphocyte count and viral load and any of the neurocognitive variables. However, in the HIV-infected group, CD4 lymphocyte count was significantly correlated with left frontal lobe volume (p=0.029). There was no association between viral load and any of the brain regions of interest.

For the whole sample (N=124), homogeneity of slopes ANCOVA controlling for age, education and intracranial vault revealed a number of significant group-dependent associations between brain volumes and neurocognitive variables. Significant associations were evident between the left frontal lobe and Trails Making Test A (p=0.04), right ACC and Grooved Pegboard Test (p=0.01) and WAIS-III Digit Symbol (p=0.04), left hippocampus and Hopkins Verbal Learning Test (HVLT) (p=0.03) and Category Fluency Test (p=0.04), corpus callosum and Controlled Oral Word Association Test (COWAT) (p=0.01), WAIS-III Digit Symbol (p=0.01) and WMS-III Spatial Span (p=0.01), left amygdala and WAIS-III Digit Symbol (p=0.01) and Colour Trails 2 (p=0.02), right amygdala and COWAT (p=0.04), left caudate and WAIS-III Digit Symbol (p=0.03), Stroop Colour Word Test (p=0.01) and Paced Auditory Serial Addition Task (PASAT) (p=0.02), respectively. Mean plots revealed that for all neurocognitive variables listed above, HIV-positive women with trauma performed more poorly (i.e. had lower mean scores or higher mean scores on tests where higher scores indicate poorer performance) than their HIV-positive counterparts without trauma and their HIV-negative counterparts with and without trauma (see Tables 3 and 4).

Discussion

The results of the present study demonstrated significant group volumetric differences for the right ACC, bilateral hippocampi, corpus callosum, left and right caudate and left and right putamen. Mean volumes of the above-mentioned regions were smallest in HIV-positive women with childhood trauma compared to all other groups. Mean volumes of the left and right amygdala were also smallest in HIV-positive women

Table 1 Socio-demographic and clinical characteristics of HIV-positive women with and without childhood trauma and HIV-negative women with and without childhood trauma

	Total sample (*N*=124)	HIV+ trauma (*n*=32)	HIV+ no trauma (*n*=30)	HIV− trauma (*n*=31)	HIV− no trauma (*n*=31)	*F*	*p*
Age						8.557	0.000**
Mean (SD)	30.27 (7.94)	34.90 (6.60)	31.06 (6.92)	29.22 (9.02)	25.77 (6.32)		
Ethnicity							
African	120	32	28	31	29		
Coloured	4	0	2	0	2		
Education						8.904	0.000**
Mean (SD)	10.29 (1.79)	9.03 (2.20)	10.53 (1.19)	10.64 (1.58)	11.00 (1.36)		
<Grade 8	16	11	2	2	1		
>Grade 8	108	21	28	29	30		
Handedness						1.420	0.240
Left	7	1	3	0	3		
Right	117	31	27	31	28		
Home language							
Afrikaans	4	0	2	0	2		
isiXhosa	119	32	28	30	29		
Other	1	0	0	1	0		
Household income							
<R40,000/$3714	119	32	27	30	30		
>R40,000	5	0	3	1	1		
Marital status							
Single	90	26	22	20	22		
Cohabiting/married	31	5	8	9	9		
Separated/divorced	3	1	0	2	0		
Employed							
Yes	32	6	11	6	9		
No	92	26	19	25	22		
ARV treatment							
Yes	30	7	23	0	0		
No	94	9	23	31	31		
CD4 count						0.020	0.887
Mean	431.20	435.91	426.00	N/A	N/A		
SD	267.75	295.155	239.01	N/A	N/A		
Minimum	25	25	124	N/A	N/A		
Maximum	1529	1529	1053	N/A	N/A		
Viral load						0.892	0.349
Mean	116,172.08	169,754.10	62,590.07	N/A	N/A		
SD	439,037.76	605,528.30	139,822.78	N/A	N/A		
Minimum	0	0	0	N/A	N/A		
Maximum	3,200,000	3,200,000	641,937	N/A	N/A		

F analysis of variance (ANOVA), *HIV+* HIV-positive, *HIV−* HIV-negative, *African* South Africans belonging to the Black racial group, *Coloured* South Africans belonging to the mixed race group, *isiXhosa* one of the official indigenous African languages spoken in South Africa, *Afrikaans* a West Germanic language spoken natively in South Africa

**$p<0.01$

with childhood trauma compared to all other groups, although the probability value did not reach significance. The results of the present study suggest that in the dually affected group (HIV and childhood trauma), brain volumes were significantly smaller, compared to women singly affected by HIV. This finding supports our primary hypothesis that women with

Table 2 Cortical volume measurements for select brain regions obtained using Freesurfer (N=124)

Brain region (volume/mm^3)	HIV+ with trauma (n=32) M (SD)	HIV− with trauma (n=31) M (SD)	HIV+ without trauma (n=30) M (SD)	HIV− without trauma (n=31) M (SD)	p
Left frontal lobe	725.84 (174.27)	783.22 (163.14)	713.60 (126.20)	779.96 (141.11)	0.400
Right frontal lobe	988.09 (239.23)	974.19 (222.51)	912.43 (165.85)	939.77 (158.70)	0.384
Left ACC	1547.06 (410.37)	1866.45 (554.08)	1675.33 (470.46)	1596.90 (410.84)	0.076
Right ACC	1773.34 (421.83)	2020.83 (444.02)	2098.86 (557.52)	2018.03 (480.70)	0.044*
Left hippocampus	3369.50 (461.37)	3591.54 (375.08)	3829.46 (435.37)	3631.19 (362.81)	0.000**
Right hippocampus	3385.09 (426.98)	3615.00 (333.11)	3779.03 (525.48)	3551.41 (462.85)	0.004**
Corpus callosum	2731.84 (516.66)	3215.48 (534.92)	3052.36 (581.53)	3097.41 (438.96)	0.009**
Left amygdala	1266.43 (211.40)	1355.41 (210.58)	1390.33 (168.74)	1315.16 (196.04)	0.054
Right amygdala	1400.90 (247.36)	1451.58 (243.44)	1431.10 (193.84)	1410.61 (228.58)	0.569
Left caudate	3228.37 (438.61)	3564.51 (467.31)	3715.60 (501.04)	3513.22 (457.39)	0.003**
Right caudate	3459.56 (433.37)	3766.74 (474.05)	3885.10 (509.06)	3659.38 (429.03)	0.008**
Left putamen	5156.31 (639.81)	5872.45 (570.78)	5550.63 (768.79)	5633.74 (708.07)	0.006**
Right putamen	4999.71 (501.91)	5621.90 (619.95)	5426.06 (587.93)	5379.03 (647.67)	0.008**

HIV+ HIV-positive, *HIV−* HIV-negative, *ACC* anterior cingulate cortex

*p<0.05, **p<0.01

HIV and childhood trauma would have significantly reduced regional brain volumes (striatum, hippocampus, amygdala, corpus callosum and anterior cingulate) compared to HIV-infected women without childhood trauma. This finding is consistent with previous studies. Research conducted in single risk groups suggest that both HIV and childhood trauma separately result in reduced volumes in regions such as the ACC, hippocampus, corpus callosum, amygdala and caudate nuclei (Ances et al. 2012; Andersen et al. 2008; Bremner et al. 1997, 2003; Cohen et al. 2006, 2010a, b; De Bellis et al. 2000; Paul et al. 2008b; Seckfort et al. 2008; Stein et al. 1997; Teicher et al. 2004; Vythilingam et al. 2002). In contrast to the only available study by Clark and colleagues, who did not find any significant volumetric differences in regions of interest such as the ACC, hippocampus, caudate and putamen, we found evidence for smaller brain volumes in the right ACC, bilateral hippocampi, corpus callosum, left and right caudate and left and right putamen among dually affected women. Although only a trend was evident, we also found that mean volumes of the left and right amygdala were smaller in HIV-positive women with ELS. In contrast, Clark and colleagues reported larger amygdala volumes in HIV-positive individuals with high levels of ELS in their study (Clark et al. 2012) which differed from our own with regards to HIV disease severity and the proportion of individuals on treatment. In the Clark et al. study (Clark et al. 2012), the majority of HIV-infected participants were on antiretroviral treatment and had higher CD4 lymphocyte counts suggestive of milder disease. The mode of transmission (homosexual or heterosexual) was not reported, and the sample consisted of both males and females. The dually affected group (HIV+ with high ELS) was also smaller in size than in the present study. In the present study, HIV transmission was heterosexual, less than half of the sample was on antiretroviral therapy, and the lower group mean CD4 lymphocyte count is suggestive of greater disease

Table 3 Mean raw scores for significantly associated neurocognitive variables categorised by group

Mean raw score	HIV− no trauma (n=31)	HIV+ no trauma (n=30)	HIV+ with trauma (n=32)	HIV− with trauma (n=31)
Trail Making A*	54.61	53.56	69.12	51.58
Grooved Pegboard (non-dominant hand)*	75.58	76.66	97.12	77.51
WAIS-III Digit Symbol	53.19	49.83	36.62	51.54
HVLT learning	24.29	22.83	21.62	23.22
Category Fluency (animals)	12.64	12.16	10.65	12.67
COWAT	23.90	21.63	22.00	22.77
WMS-III Spatial Span	11.90	11.56	10.00	11.35
Color Trails 2*	116.25	117.90	135.12	112.16
Stroop (Color-Word)	34.00	30.16	23.71	30.96
PASAT	23.38	20.76	17.59	24.93

Asterisk denotes that higher scores indicate poorer performance

HIV+ HIV-positive, *HIV−* HIV-negative, *HVLT* Hopkins Verbal Learning Test, *WAIS-III* Wechsler Adult Intelligence Scale, *WMS-III* Wechsler Memory Scale, *COWAT* Controlled Oral Word Association Task (with letters FAS for English, LBS for Afrikaans and IBS for Xhosa), *Stroop* Stroop Color and Word Test, *PASAT* Paced Auditory Serial Addition Test

Table 4 Childhood Trauma Questionnaire (CTQ) scores (N=124)

Group		Physical abuse	Sexual abuse	Emotional abuse	Emotional neglect	Physical neglect	CTQ total
HIV− no trauma (n=31)	Mean	5.22	5.00	6.87	7.48	6.61	31.19
	Min	5.00	5.00	5.00	5.00	5.00	25.00
	Max	8.00	5.00	15.00	13.00	12.00	39.00
HIV+ no trauma (n=30)	Mean	5.96	5.33	6.03	8.83	6.90	33.06
	Min	5.00	5.00	5.00	5.00	5.00	25.00
	Max	10.00	9.00	12.00	19.00	13.00	40.00
HIV+ with trauma (n=32)	Mean	15.65	10.68	17.43	16.90	15.31	76.00
	Min	5.00	5.00	9.00	8.00	5.00	54.00
	Max	44.00	25.00	25.00	25.00	24.00	110.00
HIV− with trauma (n=31)	Mean	10.06	8.35	15.48	11.87	9.96	55.74
	Min	5.00	5.00	5.00	5.00	5.00	41.00
	Max	25.00	25.00	71.00	25.00	18.00	116.00

Min minimum, *Max* maximum, *HIV+* HIV positive, *HIV−* HIV negative

severity. The present study also included an all-female sample. The aforementioned differences between the two studies make comparisons difficult; thus, future studies investigating the volumetric effects of the dual burden of HIV and ELS on the amygdala in particular are needed. In the present study, perhaps greater childhood trauma severity may have rendered the trend in amygdala differences between groups significant.

Results of the present study suggest that ICV was significantly associated with physical neglect on the CTQ. A significant positive correlation was found between ICV and childhood physical neglect. Moreover, although just shy of significance (p=0.05), a positive correlation was also evident between ICV and childhood physical abuse. This finding is to some extent similar to a previous study although there are differences in the direction of the relationship (Fennema-Notestine et al. 2002). In that study, supratentorial cranial vault was negatively correlated with the severity of childhood physical abuse in a sample of female victims of IPV (Fennema-Notestine et al. 2002). Although there was no significant difference in ICV between the groups in the current study, a larger mean ICV was evident in both the dually affected group (HIV+ trauma) and the traumatised control group (HIV− trauma), compared with the HIV-positive and HIV-negative non-traumatised groups. In addition, the mean score for childhood physical neglect and abuse was highest in the dually affected group, followed by the HIV-uninfected group with ELS. Thus, it may be possible that increased ICV in these women may be a neurodevelopmental epiphenomenon, perhaps as a result of increased levels of childhood physical abuse/neglect. However, causal inferences are not possible, and this hypothesis needs to be examined in future work.

Associations between regional brain volumes and neurocognitive variables (grouped by domain) revealed significant associations between the left frontal lobe and speed of information processing, right ACC, motor skills and processing speed, left hippocampus, learning and language/verbal fluency, corpus callosum, language/verbal fluency, processing speed and attention/working memory, left amygdala, processing speed and abstraction/executive functioning, right amygdala and language/verbal fluency, left caudate, processing speed, abstraction/executive functioning and attention/working memory, respectively. Women singly affected by HIV performed more poorly on the majority of these tasks than their HIV-negative counterparts, except on three tasks measuring processing speed, attention/working memory and motor skills (WAIS-III Digit Symbol, Trail Making Test A and Grooved Pegboard Test). For motor skills and attention/working memory (Trail Making Test A and Grooved Pegboard Test), women dually affected (HIV-positive with trauma) performed the worst, followed by HIV-negative women with trauma. These findings provide evidence for the potential contributory role of childhood trauma to brain alterations and neurocognitive decline in HIV-infected individuals. Mean scores revealed that dually affected women (HIV-positive with childhood trauma) performed the worst across all three groups on all except one task of verbal fluency (COWAT), on which HIV-positive women without trauma had a slightly lower mean score. The finding that dually affected women performed more poorly on these tasks than all other groups provides support for our second hypothesis that among those dually affected, brain volumetric differences would be consistent with poorer neurocognitive functioning.

HIV is frequently associated with deficits in higher order brain function, including memory (learning), psychomotor speed, executive functions and attention (Grant 2008). Studies have reported a link between neurocognitive impairment and alterations in brain structure, function and metabolite concentrations in HIV-infected individuals (Castelo et al.

2006; Cohen et al. 2010a; Harezlak et al. 2011; Melrose et al. 2008; Moore et al. 2006; Paul et al. 2008b). Similarly, studies have documented trauma-related neurocognitive impairments in executive functions, memory, intellectual development, language, verbal learning, spatial working memory and psychomotor speed (Choi et al. 2009; Clark et al. 2003; Jelinek et al. 2006; Lagarde et al. 2010; Majer et al. 2010; Palmer et al. 1997). Larger amygdala volumes in HIV-infected individuals with high levels of ELS were recently reported to be associated with greater impairment on the WAIS-III Digit Symbol Test, a test of processing speed (Clark et al. 2012). In keeping with this, the results of the present study also revealed an association between the amygdala and the WAIS-III Digit Symbol Test, a test of speed of information processing. Although there was no significant difference between groups on amygdala volume (only a trend), mean amygdala volume was smallest in the dually affected group (HIV+ with trauma). Moreover, performance on the WAIS-III Digit Symbol Test was poorest in this group compared to all other groups. The findings of both Clark et al. and the present study therefore suggest that HIV and ELS interact to influence amygdala volume, which is associated with neurocognitive dysfunction in individuals infected with HIV. However, as previously alluded to, this hypothesis warrants further investigation given the discrepancies between these two studies and the paucity of research on this topic. In addition to the amygdala findings, the present study also found evidence for an association between the left frontal lobe, right ACC, corpus callosum and left caudate and processing speed. The dually affected group had lower scores (i.e. worse performance) on tests of processing speed compared to all other groups, and this was significantly associated with the above-mentioned brain regions.

A limitation of the present study was the retrospective assessment of childhood trauma and its contribution to recall bias. A prospective study will better explain the effects of childhood trauma on the brain. Moreover, the CTQ-SF does not include any questions around whether the abuse reported was a single isolated event(s) or repeated exposures. This would be important to elucidate going forward. There was a difference in antiretroviral therapy among groups with more women on antiretroviral treatment in the trauma group compared with infected women without trauma. The influence that this difference in treatment status has on findings needs further exploration. Moreover, the length of antiretroviral treatment and time since HIV infection was also not taken into account and should be explored in follow-up studies. Stratification of groups on these variables would require large sample sizes. Despite these limitations, this is to our knowledge only the second study to provide evidence of a combined impact of HIV and childhood trauma on brain volumetrics and associated neurocognitive performance and the first to do so in an all-female cohort with more advanced disease.

Conclusion

The present study found evidence for smaller volumes in the right ACC, bilateral hippocampi, corpus callosum, left and right caudate and left and right putamen in HIV-infected women with childhood trauma. Although causality cannot be inferred, findings also suggest that alterations in the left frontal lobe, right ACC, left hippocampus, corpus callosum, left and right amygdala and left caudate may be associated with poorer neurocognitive performance in the domains of processing speed, attention/working memory, abstraction/executive functions, motor skills, learning and language/fluency with these effects more pronounced in women living with both HIV and childhood trauma. This highlights the potential contributory role of developmental trauma in brain morphological and neurocognitive aberrations in HIV-infected individuals. Future longitudinal studies that track the course of neurocogntive and brain volumetric changes are needed to provide more clarity.

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Conflict of interest We have no conflict of interest to declare.

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