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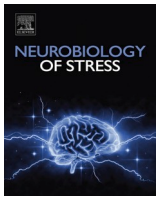

Frontal cortical volume deficits as enduring evidence of childhood abuse in community adults with AUD and HIV infection comorbidity

Stephanie A. Sassoon [a,b,*], Rosemary Fama [a,b], Kilian M. Pohl [b], Adolf Pfefferbaum [a,b], Edith V. Sullivan [b]

[a] Biosciences Division, Center for Health Sciences, SRI International, Menlo Park, CA, USA
[b] Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA

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ABSTRACT

Background: Childhood abuse is an underappreciated source of stress, associated with adverse mental and physical health consequences. Childhood abuse has been directly associated with risky behavior thereby increasing the likelihood of alcohol misuse and risk of HIV infection, conditions associated with brain structural and functional deficits. Here, we examined the neural and behavioral correlates of childhood trauma history in alcohol use disorder (AUD), HIV infection (HIV), and their comorbidity (AUD+HIV).

Methods: Occurrence of childhood trauma was evaluated by retrospective interview. Cortical (frontal, temporal, parietal, and occipital), subcortical (hippocampus, amygdala), and regional frontal volumes were derived from structural MRI, adjusted for intracranial volume and age. Test scores of executive functioning, attention/working memory, verbal/visual learning, verbal/visual memory, and motor speed functional domains were standardized on age and education of a laboratory control group.

Results: History of childhood abuse was associated with smaller frontal lobe volumes regardless of diagnosis. For frontal subregional volumes, history of childhood abuse was selectively associated with smaller orbitofrontal and supplementary motor volumes. In participants with a child abuse history, poorer verbal/visual memory performance was associated with smaller orbitofrontal and frontal middle volumes, whereas in those without childhood abuse, poorer verbal/visual memory performance was associated with smaller orbitofrontal, frontal superior, and supplemental motor volumes.

Conclusions: Taken together, these results comport with and extend the findings that childhood abuse is associated with brain and behavioral sequelae in AUD, HIV, and AUD+HIV comorbidity. Further, these findings suggest that sequelae of abuse in childhood may be best conceptualized as a spectrum disorder as significant deficits may be present in those who may not meet criteria for a formal trauma-related diagnosis yet may be suffering enduring stress effects on brain structural and functional health.

1. Introduction

Child abuse, an underappreciated source of stress, is confirmed in only 1–2 percent of victims (Pomerantz, 2018), suggesting underreporting, given that it is estimated that upwards of one-third of children may actually have experienced maltreatment before age 18 years (Bremner, 2002). As many as 5 percent of boys and 5–10 percent of girls experienced penetrative sexual abuse while the estimates of children experiencing any type of sexual abuse may be 3 times higher (Gilbert et al., 2008). The World Health Organization reports that approximately 1 in 5 women and 1 in 13 men report having experienced sexual abuse before age 18 years (World Health Organization Fact Sheet on Child Maltreatment, 19 September 2022; https://www.who.int/news-room/fact-sheets/detail/child-maltreatment), and the CDC estimates that 1 in 7 children experienced child abuse annually in the United States (Center for Disease Control and Prevention Fast Facts: Preventing Child Abuse and Neglect, 6 April 2022; https://www.cdc.gov/violenceprevention/childabuseandneglect/fastfact.html) although the CDC recognizes that statistics may be underestimated due to underreporting (Leeb et al., 2008).

Childhood maltreatment is well known to have profound consequences including chronic mental health problems such as complex

* Corresponding author. Biosciences Division, Neuroscience Program, SRI International, 333 Ravenswood Ave., BN-165, Menlo Park, CA, 94025, USA.
E-mail address: stephanie.sassoon@sri.com (S.A. Sassoon).

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post-traumatic stress disorder (Leiva-Bianchi et al., 2023), illegal behavior, obesity, physical health problems including heart disease, respiratory disease, cancer, and curtailed life expectancy (Hughes et al., 2017). Moreover, abuse during childhood can increase the likelihood of risky behavior (Bounoua and Sadeh, 2022) leading to alcohol and substance use disorders and risky sexual behavior, increasing the risk of acquiring human immunodeficiency virus (HIV) infection (Hughes et al., 2017; Patock-Peckham et al., 2020; Troeman et al., 2011). This cascade of negative consequences from childhood trauma leading to substance dependence and acquisition of HIV infection creates an enormous psychological, social, and economic burden (Bingham et al., 2021; Gelles and Perlman, 2012; Sacks et al., 2015).

Recognizing that childhood through adolescence is a critical time for brain development [for review (Giedd and Rapoport, 2010)], abuse during those formative years may lead to reprogramming and dysfunction of the body's stress response system and has been associated with alterations in brain regions susceptible to stress (Kirsch and Lippard, 2022). Moreover, abuse during childhood may negatively impact cognition and behavior. How childhood abuse affects the brain and behavior is a complex process influenced by such parameters as age and developmental period during which trauma occurs, the type and severity of abuse, and the sex of the victim (Kavanaugh et al., 2017). Particular brain regions in adults found to be affected by child abuse involve cortical regions, including auditory, visual, and somatosensory cortex, frontal lobe subregions including orbitofrontal and dorsal lateral prefrontal cortices, and subcortical structures including the hippocampus and amygdala (Ahmed-Leitao et al., 2016; Hart and Rubia, 2012; Paquola et al., 2016; Teicher and Samson, 2016). Neuropsychological studies of adults who experienced maltreatment during childhood have found child abuse to be associated with deficits in executive functioning (Gould et al., 2012) including inhibitory control (Hart and Rubia, 2012), in memory, including short- and long-term verbal and visual and working memory (Hart and Rubia, 2012), and in processing speed in adults with PTSD (Scott et al., 2015).

Fewer studies have examined the effects of childhood trauma in adult cohorts with AUD, HIV, or their comorbidity. According to recent prevalence data from the CDC, more than half of people living with HIV infection in the United States and territories were aged 50 or older (Center for Disease Control HIV Surveillance Report: Diagnoses of HIV Infection in the United States and Dependent Areas, 2021, https://www.cdc.gov/hiv/library/reports/hiv-surveillance/vol-34/index.html). Improvements in the effectiveness of antiretroviral therapy affords those with HIV infection a near-normal life expectancy, which also means that some persons living with HIV infection may engage in or continue hazardous alcohol use. Similar to childhood trauma, general HIV-associated cognitive sequelae include dysfunction in psychomotor speed, executive function, and memory (Giesbrecht et al., 2014; Heaton et al., 2011). While the literature on cognitive sequelae in those with trauma and HIV is scant, a recent study found that childhood trauma interacting with genes responsible for dopamine transport and metabolism could be associated with the onset of HIV-associated neurocognitive disorders (HAND) (Roomaney et al., 2021) by nature of sharing common etiological mechanisms (viz., hypothalamic-pituitary-adrenal axis dysregulation, neuroinflammation, and oxidative stress) (Womersley et al., 2017). Consistent with this speculation of neuromechanisms of trauma-HIV interactions, volume deficits observed in the frontal lobe, hippocampus, corpus callosum, and amygdala have been found to be associated with poorer performance in domains of executive functioning, attention/working memory, motor skills, processing speed, and language/fluency in women with HIV infection and a history of childhood trauma (Spies et al., 2016).

Even with sustained sobriety or substantial reduction in alcohol consumption, people with AUD commonly have deficits in attention, executive function, information processing speed, episodic memory, gait and balance, and visuospatial ability (Bernardin et al., 2014; Fein et al., 1990; Sullivan et al., 2010). Older individuals with AUD are especially vulnerable to functional compromise (Rosenbloom et al., 2003). By MRI, brain volume deficits occur particularly in the frontal lobes, hippocampus, thalamus, and cerebellum (Makris et al., 2008; Pfefferbaum et al., 2018; Rosenbloom et al., 2003; Sullivan et al., 2018). Studies examining the comorbidity effects of HIV infection and AUD on brain structure and function report shrinkage, particularly in the frontal cortex (Pfefferbaum et al., 2018) with impairment in working memory, visuospatial abilities, and psychomotor speed (Rosenbloom et al., 2010). Moreover, trauma in conjunction with AUD and HIV infection comorbidity has been found to be associated with poorer episodic memory (Sassoon et al., 2017) and compromised quality of life (Sassoon et al., 2023).

Adverse childhood events were recently associated with poorer cognitive function later in life and with increased risk for dementia (Nilaweera et al., 2022; Radford et al., 2017; Schickedanz et al., 2022). Those with AUD and HIV may carry even greater risk for brain compromise and cognitive decline with senescence due to the interaction of disease burden with childhood trauma.

Most studies reporting brain alterations with trauma have examined adults with PTSD. It is less known how a history of childhood abuse affects adults, particularly those with a history of AUD or HIV infection, who are not necessarily reporting current acute symptoms of trauma-related anxiety. To address these unknowns in adults with AUD or HIV, the aims of this study were to examine brain volumes derived from MRI of the four cortical lobar regions (frontal, parietal, temporal, occipital) and two subcortical regions (hippocampus and amygdala) and to examine data from cognitive and motor assessments to test two primary hypotheses regarding neurobiological basis of trauma-related stress: (1) child abuse would be associated with smaller frontal lobe, amygdala, and hippocampal volumes in cohorts of community adults with AUD, HIV, and AUD+HIV comorbidity with history of childhood abuse compared to those without a history of childhood trauma, and (2) cognitive and motor testing would reveal greater deficits in adults with AUD, HIV, and AUD+HIV comorbidity with a history of childhood abuse relative to counterparts without a history of childhood trauma. Exploratory analyses investigated whether subregions of the frontal lobe were differentially sensitive to history of childhood trauma.

2. Method

2.1. Participants

A total of 298 participants, recruited between 2004 and 2020 as part of an ongoing longitudinal study examining the effects of HIV infection and alcohol on brain structure and function, were included in this study. Participants were recruited from the greater San Francisco Bay area through presentations about the study at transitional sober living environments, community treatment programs, or support group meetings, referrals from medical centers, response to flyers or internet postings, outreach at community functions such as AIDS Walk, or through word of mouth. Procedures were reviewed and approved by the Institutional Review Boards of SRI International (Advarra IRB) and Stanford University School of Medicine.

The 298 participants were stratified based on 3 categories: (a) presence of DSM-IV-TR alcohol dependence/abuse and/or DSM-5 alcohol use disorder (AUD) history (yes/no), (b) presence of HIV infection (yes/no), and (c) history of childhood abuse (yes/no). This yielded 8 diagnostic groups of participants: (1) AUD+HIV+Ab: 28 HIV-positive participants who met DSM-IV-TR/DSM-5 lifetime AUD and had a history of childhood abuse; (2) AUD+HIV+nAb: 26 HIV-positive participants who met criteria for lifetime AUD and had no history of childhood abuse; (3) HIV+Ab: 24 HIV-positive participants with history of childhood abuse who never met criteria for AUD; (4) HIV+nAb: 28 HIV-positive participants without a history of childhood abuse and who never met criteria for AUD; (5) AUD+Ab: 49 HIV-negative participants who met criteria for AUD with history of childhood abuse; (6)

AUD+nAb: 66 HIV-negative participants who met criteria for AUD without history of childhood abuse; (7) CTL+Ab: 20 HIV negative participants who have history of childhood abuse but no lifetime history of AUD (healthy controls with childhood abuse history); and (8) CTL+nAb: 57 HIV-negative participants who neither had history of childhood abuse nor met criteria for AUD (healthy controls without childhood abuse history). See Table 1 for demographic data.

2.2. Procedure

After providing verbal consent, potentially interested participants were initially screened by telephone interview. Participants passing the initial screening process were invited to the laboratory for a detailed clinical assessment involving a psychiatric and medical history, blood draw, neuropsychological assessment, and MRI scan. Participants provided written informed consent for study participation and were then screened by breathalyzer to ensure a breath alcohol level of 0.0.

2.3. Clinical interview for AUD status and childhood abuse history

Participants underwent psychiatric and substance use assessment by senior clinical staff using the Structured Clinical Interview for DSM-IV-TR (SCID) (First et al., 2002). Exclusion criteria were lifetime history of schizophrenia or bipolar disorder, and/or presence of dependence or abuse of substances other than alcohol, nicotine, or cannabis that exceeded length of alcohol use disorder history, or which began prior to

Table 1
Demographics of the participant groups (N = 298).

n =	CTL	CTL	AUD	AUD	HIV	HIV	AUD+HIV	AUD+HIV	*p value*
	No Abuse	Abuse	No Abuse	Abuse	No Abuse	Abuse	No Abuse	Abuse	
	57	20	66	49	28	24	26	28	
	% or Mean (SD)	% or Mean (SD)	% or Mean (SD)	% or Mean (SD)	% or Mean (SD)	% or Mean (SD)	% or Mean (SD)	% or Mean (SD)	
Background demographics									
Sex (% Men)	61.40%	50.00%	74.20%	69.40%	67.90%	75.00%	73.10%	50.00%	0.20
Age	55.37 (12.69)	55.48 (14.49)	54.57 (9.40)	50.33 (10.06)	55.33 (9.66)	54.34 (10.00)	55.49 (7.54)	54.38 (5.64)	0.27
Education (yrs)	16.33 (2.48)	15.70 (2.18)	13.65 (2.66)	13.02 (2.50)	13.64 (2.50)	13.79 (2.93)	13.08 (2.04)	13.57 (2.19)	<0.001 [CTL > AUD, HIV, AUD + HIV]
Ethnicity (% Non-Cau.)	45.61%	50.00%	65.15%	53.06%	53.57%	37.50%	88.46%	78.57%	<0.001 [AUD + HIV > AUD, HIV, CTL]
Socioeconomic Status (SES)[a]	24.18 (11.78)	26.95 (11.15)	41.48 (17.42)	42.92 (15.82)	38.96 (16.04)	35.88 (13.32)	42.08 (13.80)	41.86 (14.24)	<0.001 [CTL < AUD, HIV, AUD + HIV]
Lifetime Substance Use Disorder (%)	0.00%	0.00%	66.67%	81.63%	39.29%	37.50%	73.08%	71.43%	<0.001 [CTL < HIV < AUD = AUD + HIV]
Drug Abuse Remission (months)[b]	–	–	135.48 (146.82); 73	95.99 (113.49); 33	126.43 (119.91); 91	164.44 (168.55); 98	95.04 (98.04); 69	123.45 (121.58); 80	0.81 (CTL not incl.)
Childhood abuse history									
Childhood Abuse History (%)		25.97%		42.61%		46.15%		51.85%	0.02 [CTL < AUD, HIV, AUD + HIV]
Childhood Abuse Age of Onset		8.45 (4.10)		6.76 (3.70)		7.00 (4.05)		8.11 (4.14)	0.28
Number of Childhood Abuse Events[b]		74 (102); 34		131 (115); 100		136 (129); 101		149 (146); 107	0.20
Lifetime PTSD diagnosis (%)	0%	0%	3 (4.54%)	2 (3.03%)	0%	3 (12.5%)	1 (3.85%)	4 (12.3%)	
AUD-related demographics									
AUD Age of Onset	–	–	27.88 (9.83)	24.63 (10.54)	–	–	22.04 (6.42)	25.54 (10.44)	0.06
AUD Sobriety (months)[b]	–	–	13.84 (81.72); 1.94	2.99 (2.53); 2.01	–	–	10.68 (25.79); 0.23	14.62 (50.12); 0.13	0.04[c] (AUD > AUD + HIV)
AUDIT Score[b]	2.39 (1.94); 2	1.65 (1.50); 2	16.62 (10.08); 15	21.50 (10.77); 23	2.00 (1.84); 2	1.72 (1.99); 1	8.32 (10.58); 3	13.96 (10.37); 14	<0.001 [CTL = HIV < AUD + HIVnt < AUD + HIVt = AUD]
Lifetime Alcohol Consumption (kg)[b]	47 (70); 20	35 (48); 9	1244 (1014); 880	1343 (1037); 990	97 (129); 44	46 (48); 36	980 (685); 871	1036 (1205); 580	<0.001 [(CTL = HIV) < (AUD = AUD + HIV)]
HIV-related demographics									
HIV Age of Onset	–	–	–	–	36.18 (8.84)	32.29 (9.48)	34.72 (8.63)	35.02 (6.73)	0.47
Length of time with HIV (years)	–	–	–	–	18.92 (9.43)	21.00 (8.86)	20.24 (6.58)	19.42 (6.79)	0.82
AIDS Status (%)	–	–	–	–	53.57%	45.83%	65.38%	60.71%	0.73
HAART Medications (%)	–	–	–	–	85.71%	87.50%	92.31%	92.86%	0.93
Log Viral Load	–	–	–	–	2.21 (1.23)	1.71 (0.70)	1.98 (1.04)	2.05 (1.21)	0.48
CD4 T Lymphocyte Count[b]	–	–	–	–	575 (256); 524	634 (249); 670	589 (349); 566	641 (365); 713	0.83

[a] Lower value = higher SES.
[b] Mean (SD); median.
[c] Comparison of medians.

AUD at study entry. Participants in the alcohol use disorder (AUD) groups met lifetime DSM-IV-TR criteria for alcohol dependence/abuse and/or DSM-5 criteria for AUD. As part of the clinical interview, participants were queried about their medical history and medication usage, including information about acquisition of HIV. A history of chemotherapy, injury affecting the central nervous system including a loss of consciousness >30 min, stroke, epilepsy, uncontrolled diabetes, and ferrous metal in the body precluding MRI scanning were additional exclusions.

A semi-structured lifetime alcohol history timeline follow-back interview provided information regarding sobriety and an estimation of total quantity of alcohol consumed over the lifetime, in which drinks of each type of alcoholic beverage (beer, wine, spirit) was standardized to units containing approximately 13.6 g of absolute alcohol. (Skinner, 1982; Skinner and Sheu, 1982). Participants were also administered the Alcohol Use Disorder Identification Test (AUDIT) (Babor et al., 2001), a 10-item screening instrument to identify hazardous alcohol consumption. Irrespective of childhood abuse history, the four AUD groups (AUD with and without abuse and AUD+HIV with and without abuse) had marginally different ages of onset for alcohol diagnoses ($p = 0.06$), with AUD+HIV without trauma having the youngest age of onset at about 22 years old and AUD without trauma having the oldest age of onset at 27 years old. Comparison of median length of sobriety indicated that those with AUD+HIV were more likely to have more recent sobrieties than those with only AUD ($p = 0.04$) but consumed relatively equivalent amounts of alcohol over their lifetimes, significantly more than those in groups without AUD ($p < 0.001$); by AUDIT, groups with AUD had the highest alcohol risk over the past year ($p < 0.001$).

Historical trauma information was collected by experienced senior research staff through in-person interview (see (Turner and Lloyd, 2004)). Childhood abuse was defined herein as a positive endorsement of experiencing ≥1 of 8 traumas before the age of 18 (Turner and Lloyd, 2004). Trauma types included 2 categories of sexual abuse (rape, molestation), 4 categories of physical abuse (physical abuse by parents/guardians, boyfriend/girlfriend/partner, by someone else known to them, physical assault/mugging), emotional abuse, or witnessed mother or another close female relative being regularly physically or emotionally abused. For further information regarding procedures, see (Sassoon et al., 2017). The type of child abuse participants reported having experienced is summarized in Table 2.

Table 2
Types of childhood abuse experienced by participants with an abuse history (N = 121 of 298).

Types of Childhood Abuse Experienced[a]	CTL with Abuse (n = 20 of 77)	AUD with Abuse (n = 49 of 115)	HIV with Abuse (n = 24 of 52)	AUD+HIV with Abuse (n = 28 of 54)
Forced sexual intercourse	3 (15%)	8 (16%)	5 (21%)	13 (46%)
Forced sexual touching	8 (40%)	15 (31%)	6 (25%)	13 (46%)
Physical abuse by parent/guardian	8 (40%)	22 (45%)	12 (50%)	8 (29%)
Physical abuse by boyfriend/girlfriend	2 (10%)	2 (4%)	1 (4%)	3 (11%)
Physical abuse by someone else	2 (10%)	6 (12%)	1 (4%)	5 (18%)
Physically assaulted or mugged	2 (10%)	6 (12%)	2 (8%)	6 (21%)
Emotional abuse by a parent, guardian, caretaker	7 (35%)	25 (51%)	13 (54%)	9 (32%)
Witnessed mother/female relative regularly abused	11 (55%)	29 (59%)	10 (42%)	17 (61%)

[a] Many participants reported experiencing >1 type of abuse.

2.4. Hematological analysis for HIV status

Participants contributed blood samples from which antibody tests confirmed HIV status. For those who were positive for HIV, CD4 T lymphocyte count and viral load parameters were provided. All participants had a Karnofsky score of ≥70 (Karnofsky, 1949). Irrespective of abuse history, the HIV and AUD+HIV groups had similar mean ages of onset of HIV infection ($p = 0.47$), length of time with HIV infection ($p = 0.82$), proportions with AIDS status ($p = 0.73$), and proportions on highly active anti-retroviral medications (HAART; $p = 0.93$). Moreover, those in groups with HIV infection had similar $\log_{10}$ viral loads ($p = 0.48$) and CD4 T lymphocyte counts ($p = 0.83$).

2.5. Neuropsychological testing

Participants received a battery of standard cognitive and motor tests comprising composites of functional domains:

Executive Function Composite ($n = 286$): (1) Trails B time from the Trail Making Test (Reitan, 1958) or Color Trails 2 time from the Color Trails Test (D'Elia et al., 1996), (2) Digit Symbol raw score of the Wechsler Adult Intelligence Scale-Revised (Wechsler, 1981) or the Symbol Digit Test raw score (Smith, 1982), and (3) the F-A-S Verbal Fluency Test total score (Benton and Hamsher, 1976).

Attention and Working Memory Composite ($n = 293$): (1) Trails A time from the Trail Making Test (Reitan, 1958) or Color Trails 1 time from the Color Trails Test (D'Elia et al., 1996), (2) Digit span forwards and backwards from the Wechsler Memory Scales-Revised (WMS-R) (Wechsler, 1987) or Digits Forwards and Backwards subtests from the MicroCog (Elwood, 2001), and (3) Block span forwards and backwards from the WMS-R (Wechsler, 1987).

Verbal and Visual Learning Composite ($n = 288$): (1) Immediate Recall raw score from the Rey-Osterrieth Complex Figure Test (Osterrieth and Rey, 1944; Rey, 1942) and (2) Logical Memory I raw score from the WMS-R (Wechsler, 1987) or Stories-Immediate Recall score from the MicroCog (Elwood, 2001).

Verbal and Visual Memory Composite ($n = 288$): (1) Delayed Recall raw score from the Rey-Osterrieth Complex Figure Test (Osterrieth and Rey, 1944; Rey, 1942) and (2) Logical Memory II raw score from the WMS-R (Wechsler, 1987) or Stories-Delayed Recall score from the MicroCog (Elwood, 2001).

Motor Speed Composite ($n = 284$): (1) Grooved Pegboard Test mean of left and right hand times (Lafayette Instruments, Lafayette, IN), (2) Finger Tapping Test mean of left hand and right hand unimanual scores (Reitan and Davison, 1974), and (3) Fine Finger Movement Test mean of all conditions (Corkin et al., 1986).

Composite scores comprised means of all available tests within that composite for each participant. Some test results (such as timed tests, Trails A & B) were transformed so that across all tests, higher scores represented better performance. Test scores were converted to standardized age-corrected z-scores based on data from 55 male and 47 female, healthy control participants from laboratory studies, mean age 47.9 ± 14.9 years, with mean of 15.8 ± 2.4 years of education. For more details about administration of the cognitive tests, please see (Sassoon et al., 2017).

2.6. MRI acquisition

Brain MRI data on all 298 participants were acquired using a 3-T GE Discovery MR750 system (General Electric Healthcare, Waukesha, WI) using an 8-channel phased-array head coil. T1-weighted Inversion-Recovery Prepared SPoiled Gradient Recalled (SPGR) images (TR = 6.55/5.92 ms, echo time TE = 1.56/1.93 ms, TI = 300 ms, matrix 256 × 256, thick = 1.25 mm, skip = 0 mm, 124 slices) were based on a structural sequence that was used for volumetric analysis. For a complete description of preprocessing and parcellation procedures, please see (Fama et al., 2021). All regional brain volumes were age- and

intracranial volume-corrected based on 238 laboratory controls (19–86 years old) and were calculated using the SRI24 atlas (Rohlfing et al., 2010) to delineate cortical (frontal, temporal, parietal, and occipital) and subcortical volumes (hippocampus and amygdala). The frontal region was additionally parcellated into seven regions of interest (ROIs): precentral, superior, orbitofrontal, middle, inferior, supplemental motor, and medial. In this study, brain ROIs examined included the four cortical regions, the 7 frontal subregions, and 2 subcortical regions: the hippocampus and amygdala. Fig. 1 shows the parcellation of the frontal region into 7 subregions.

2.7. Statistical analyses

For demographic data analyses, chi-square tests and Fisher's exact tests compared proportions among the 8 groups. Group comparisons of continuous demographic data were conducted by one-way ANOVAs or factorial ANOVAs (four diagnostic groups by abuse (yes/no) followed by paired t-tests for specific group comparisons, and group comparisons of data with limited ranges or non-normal distributions were analyzed with Kruskal-Wallis tests or Mann-Whitney U tests.

For main analyses, 2×2×2 ANCOVAs (AUD diagnosis: yes/no; HIV diagnosis: yes/no; childhood abuse history: yes/no), controlling for sex, age, race (Caucasian yes/no), and socioeconomic status, with Sheffé post-hoc follow-up tests, were conducted on regional brain volumes and neuropsychological test composite data. Pearson correlations tested relationships between demographic and disease-related variables and the dependent variables, namely, brain volumes and behavioral performance on cognitive test components. Statistical analyses were conducted with SPSS Statistics Version 29 (Released 2022. IBM SPSS Statistics for Windows, Version 29.0. Armonk, NY: IBM Corp.).

3. Results

3.1. Demographic data

Demographic data for the clinical groups (AUD, HIV, and AUD+HIV) and the control group by presence of childhood abuse history are presented in Table 1. Groups were relatively matched with regards to sex and age. Irrespective of trauma, controls had more years of education ($p < 0.001$) and had a higher socioeconomic status ($p < 0.001$) than those in clinical groups. Also irrespective of trauma, AUD+HIV groups had more participants of minority ethnic background than other groups ($p < 0.001$). Within each group, the proportion of men and women with childhood abuse did not statistically differ (AUD: Chi-square $p = 0.754$; HIV: Fisher's Exact Test $p = 0.621$; AUD+HIV: Fisher's Exact Test $p = 0.103$; CTL: Fisher's Exact Test $p = 0.170$).

All of the 115 AUD participants met DSM-IV-TR criteria for Alcohol Dependence. Of the 32 AUD participants with additional DSM-5 diagnoses, none had mild AUD; all had moderate or greater AUD severity. Of the 54 AUD+HIV participants, 8 had DSM-IV-TR Alcohol Abuse, while 46 had Alcohol Dependence. Of the 8 AUD+HIV participants with additional DSM-5 diagnoses, 2 had mild AUD and 6 had severe AUD.

A large proportion in each diagnostic group met historical DSM-IV-TR criteria for substance abuse/dependence to sedatives, cannabis, cocaine, amphetamines, hallucinogens, and/or opiates: 67% of AUD without abuse, 82% of AUD with abuse, 39% of HIV without abuse, 38% of HIV with abuse, 73% of AUD+HIV without abuse, and 71% of AUD+HIV with abuse. Sobriety to these drugs was historically longer than that of sobriety to alcohol for all groups with AUD history.

For those with a history of childhood abuse and AUD, the abuse occurred prior to the onset of AUD in all but two participants; in two, the onset of abuse and AUD were reportedly at the same age. In all participants with abuse history and HIV infection, the abuse occurred prior to the onset of HIV infection. In only seven participants did onset of AUD precede the age of HIV infection; four had a history of childhood abuse, three did not.

Of those reporting experiencing childhood abuse, 2 with AUD, 3 with HIV, and 4 with AUD+HIV met DSM criteria for post-traumatic stress disorder (PTSD). No controls with abuse met criteria for PTSD. Three participants with AUD and 1 participant with AUD+HIV met criteria for PTSD but denied a history of childhood abuse; abuse may have occurred as an adult or may have been related to non-abuse-related trauma during childhood. Analyses were repeated with removal of these participants and results did not significantly change.

3.2. Analyses of brain MRI data

ANCOVAs on age- and head-size corrected brain volumes revealed a significant main effect of childhood abuse history on frontal lobe volumes, $F(1, 286) = 4.71$, $p = 0.03$, without a significant 2×2×2 interaction (AUD history: yes/no by HIV infection status: yes/no by childhood trauma history: yes/no) (See Fig. 2). No other significant main effects of abuse history were found for the other brain regions analyzed: parietal, temporal, occipital, hippocampal, or amygdala. Irrespective of diagnostic status, participants with history of childhood abuse had smaller frontal lobe volumes than those without abuse history. Groups with HIV infection, particularly those with abuse history, had the smallest frontal lobe volumes, $F(1, 286) = 11.90$, $p < 0.001$, relative to non-HIV groups with and without trauma.

Analysis of frontal lobe subregions yielded a significant main effect of childhood abuse on orbitofrontal cortical volumes, $F(1, 286) = 4.09$, $p = 0.04$, which was partially explained by the interaction of HIV infection on childhood abuse history in that those with both HIV infection and a history of childhood abuse had marginally smaller orbitofrontal cortical volumes, $F(1, 286) = 3.25$, $p = 0.07$ (See Fig. 3). Additionally, a significant effect of childhood abuse was found on supplemental motor cortical volumes, $F(1, 286) = 3.98$, $p = 0.047$, where groups with abuse history had smaller supplemental motor volumes (See

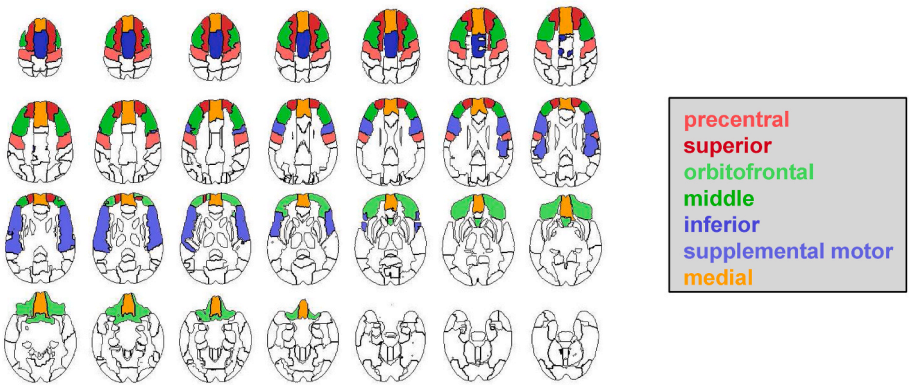

Fig. 1. 7 Frontal cortical subregions.

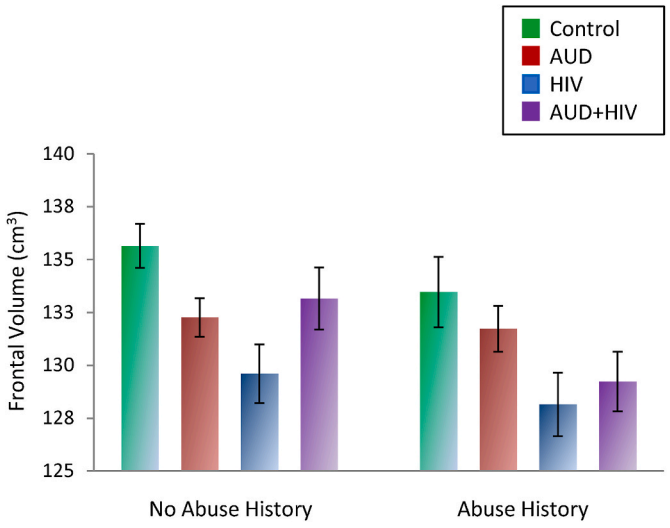

Fig. 2. Adjusted means and standard errors of frontal volumes in groups with and without a history of childhood abuse; main effects of childhood abuse history, $F(1, 286) = 4.71$, $p = 0.03$, and HIV status, $F(1, 286) = 11.90$, $p < 0.001$, on frontal lobe volumes.

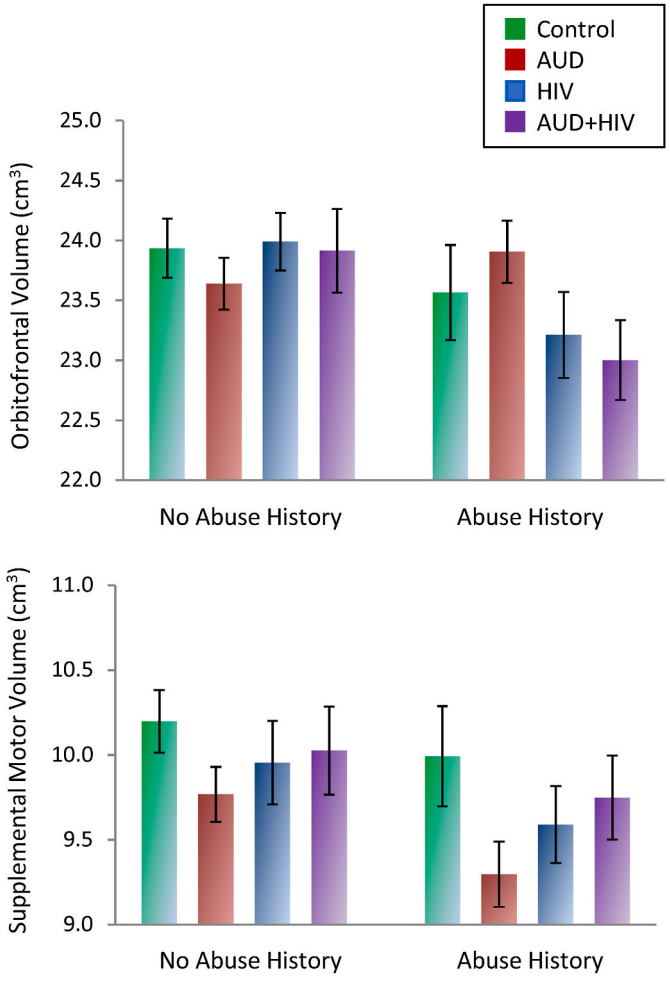

Fig. 3. Adjusted means and standard errors of orbitofrontal and supplemental motor volumes in groups with and without a history of childhood abuse; main effect of childhood abuse history on orbitofrontal volumes, $F(1, 286) = 4.09$, $p = 0.04$, and main effect of childhood abuse history on supplemental motor volumes, $F(1, 286) = 3.98$, $p = 0.047$.

Fig. 3).

In those with HIV, a higher viral load was associated with smaller frontal lobe volume [$n = 48$, $r = -0.35$, $p = 0.01$ in those with abuse history; $n = 46$, $r = -0.27$, $p = 0.07$ in those without childhood abuse history]. Additionally, in those with abuse history, a higher T-cell count was associated with larger frontal lobe volume ($n = 51$, $r = 0.30$, $p = 0.03$), particularly in the orbitofrontal subregion ($n = 48$, $r = -0.28$, $p = 0.05$). The main effect of childhood abuse history on frontal lobe volume, and on orbitofrontal subregional volume, in HIV positive participants remained significant even when controlling for differences in log viral load (frontal lobe: $p = 0.05$; orbitofrontal: $p = 0.02$) or T-cell count (orbitofrontal: $p = 0.04$).

3.3. Analyses of neuropsychological composite data

Five neuropsychological test domains were executive functioning, attention and working memory, verbal and visual learning, verbal and visual memory, and motor speed. ANCOVA yielded an interaction of AUD history status and childhood abuse history on verbal and visual memory, $F(1, 276) = 3.77$, $p = 0.05$, where groups without AUD history but with childhood abuse performed poorer on the verbal and visual memory tasks than those without childhood abuse history. In groups with AUD, there were no differences in verbal/visual memory performance between those with and without abuse history (see Fig. 4). A weak main effect of childhood abuse on motor speed was also found, $F(1, 272) = 3.60$, $p = 0.06$; those with history of childhood abuse performed more slowly on the motor speed tests than those without child abuse history (see Fig. 4). No interactions of AUD history, HIV infection status, and abuse history were found for executive function, attention and working memory, verbal and visual learning, and motor speed.

In those without childhood abuse, a greater lifetime alcohol consumption was associated with slower motor speed ($n = 168$, $r = -0.42$, $p < 0.001$) and poorer verbal/visual memory ($n = 171$, $r = -0.42$, $p <$

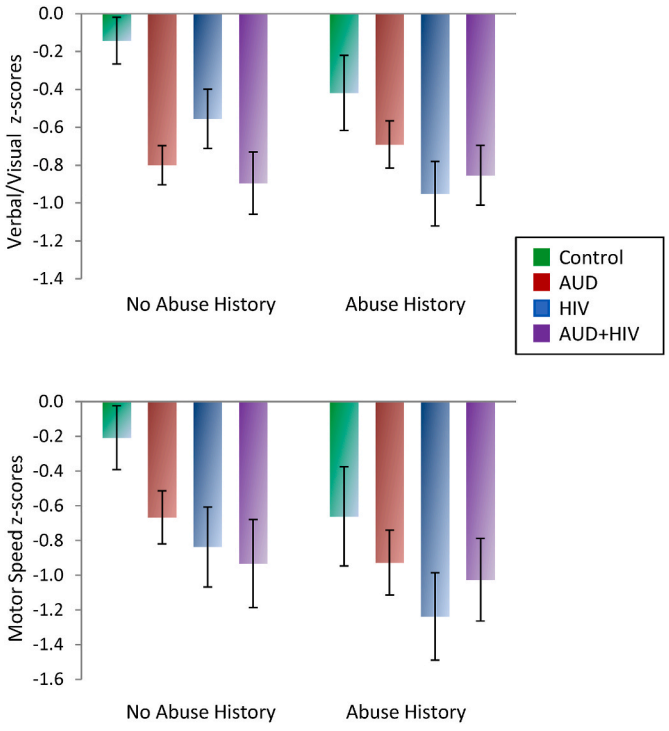

Fig. 4. Verbal/visual memory composite and motor speed composite adjusted z-score means and standard errors in groups with and without a history of childhood abuse; Interaction of AUD history and childhood abuse history on verbal/visual memory, $F(1, 276) = 3.77$, $p = 0.05$, marginal main effect of childhood abuse history on motor speed, $F(1, 272) = 3.60$, $p = 0.06$.

0.001), whereas in those with a history of abuse, greater lifetime alcohol consumption was associated with poorer verbal/visual memory (n = 117, r = −0.25, p = 0.007) but not motor speed (n = 116, r = -0.13, p = 0.16).

Slower motor speed performance was not correlated with smaller supplemental motor volumes, either in those with childhood abuse history (n = 116, r = −0.14, p = 0.15) or in those without abuse history (n = 168, r = 0.03, p = 0.68). In fact, slower motor speed was not correlated with any frontal lobe subregion in those with childhood abuse history, whereas in those without abuse history, slower motor speed was associated with smaller frontal inferior volumes (n = 168, r = 0.16, p = 0.03). In those with a child abuse history, poorer verbal and visual memory performance was associated with smaller orbitofrontal volumes (n = 117, r = 0.23, p = 0.01) and smaller frontal middle volumes (n = 117, r = 0.18, p = 0.05), whereas in those without childhood abuse history, poorer verbal and visual memory performance was associated with smaller orbitofrontal volumes (n = 171, r = 0.17, p = 0.03), smaller frontal superior volumes (n = 171, r = 0.22, p = 0.004), and smaller supplemental motor volumes (n = 171, r = 0.16, p = 0.04). Within the AUD group without a history of childhood abuse, poorer verbal and visual memory was related to smaller orbitofrontal volumes (n = 65, r = 0.25, p = 0.04), smaller superior volumes (n = 65, r = 0.28, p = 0.03), smaller precentral volumes (n = 65, r = 0.27, p = 0.03), and larger frontal middle volumes (n = 65, r = −0.27, p = 0.03), whereas in the AUD group with a history of childhood abuse, poorer verbal and visual memory performance was solely related to smaller orbitofrontal volumes (n = 47, r = 0.43, p = 0.003).

In those with childhood abuse history, poorer verbal and visual learning performance was also associated with smaller orbitofrontal volumes, (n = 117, r = 0.20, p = 0.03), whereas in those without abuse history, poorer verbal and visual learning performance was correlated with smaller frontal lobe volumes in general (n = 171, r = 0.15, p = 0.04), smaller subregional frontal superior volumes (n = 171, r = 0.24, p = 0.001), and marginally smaller supplemental motor volumes (n = 171, r = 0.15, p = 0.06).

A dissociation was found by which, in AUD with childhood abuse history, poorer verbal and visual learning performance was associated with smaller orbitofrontal volumes (n = 47, r = 0.37, p = 0.01) with no relationship between performance and frontal superior volumes (n = 47, r = 0.03, p = 0.86). By contrast, in AUD without abuse history, poorer verbal and visual learning performance was associated with smaller frontal superior volumes (n = 65, r = 0.34, p = 0.006) but not orbitofrontal volumes (n = 65, r = 0.13, p = 0.32) (See Fig. 5).

4. Discussion

The results provide partial support for our study hypotheses. For the first hypothesis predicting that child abuse would be associated with smaller frontal lobe, amygdala, and hippocampal volumes in cohorts of community adults with AUD, HIV, and AUD+HIV comorbidity with history of childhood abuse compared to those without a history of childhood abuse, we found that smaller frontal lobe volumes were associated with a history of childhood abuse. However, we did not find an effect of childhood abuse on hippocampal or amygdala volumes nor volumes of any other cortical regions. Exploratory analyses of frontal subregions did show differential sensitivity to history of childhood trauma. Specifically, adults with AUD, HIV, and AUD+HIV comorbidity with a history of childhood abuse had smaller supplemental motor and orbitofrontal volumes than those without such histories. The finding of smaller orbitofrontal volumes was partially explained by the interaction

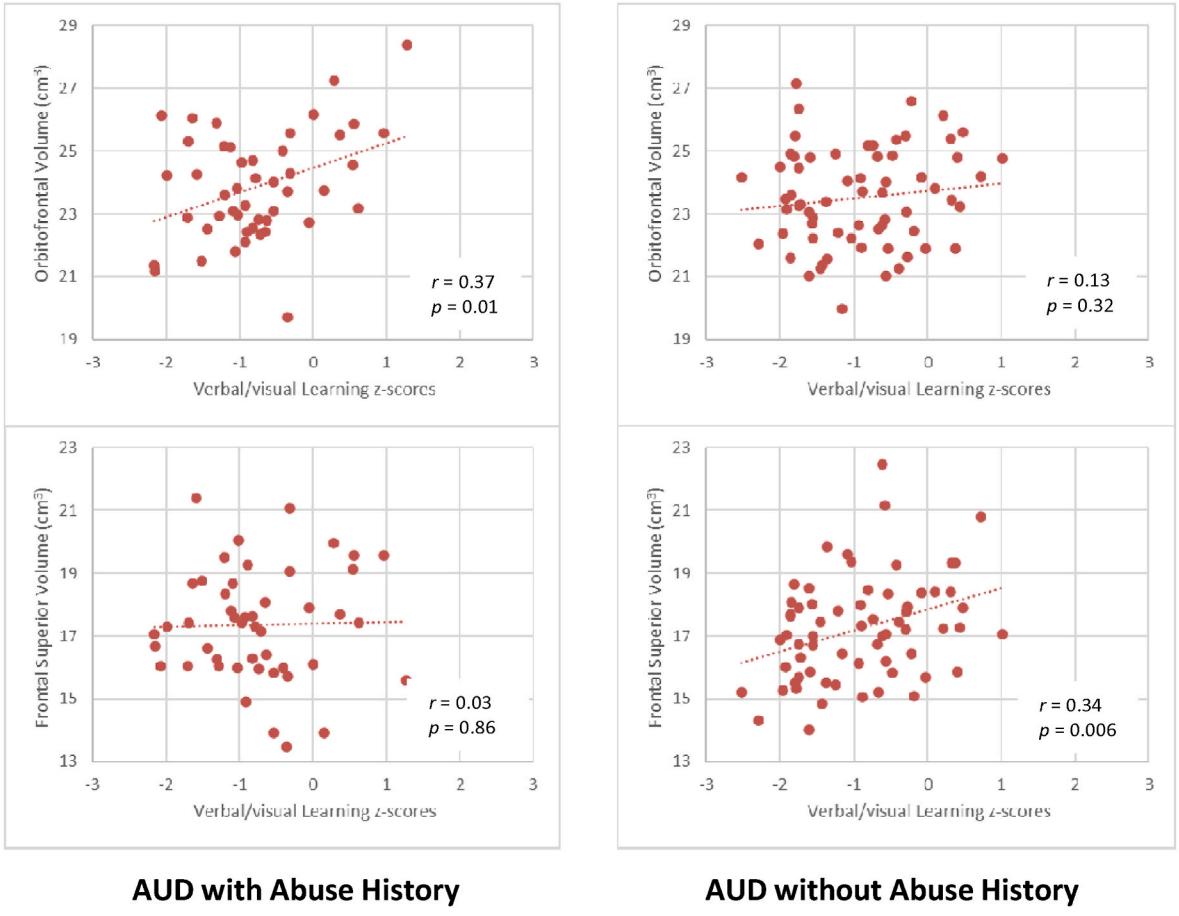

Fig. 5. Dissociation correlations among AUD with and without abuse history.

of HIV infection on childhood abuse history: individuals with both HIV infection and a history of childhood abuse had marginally smaller orbitofrontal cortical volumes than those without such histories. Although one might expect a compounded effect of AUD+HIV with a history of childhood trauma on frontal volumes, we did not find this effect.

Our findings of smaller frontal lobe volumes associated with abuse were in line with those of a study comprising two large community-based samples from the United Kingdom (Madden et al., 2023), suggesting lasting effects of abuse on brain structure, although our data did not support findings of smaller hippocampal volumes (Madden et al., 2023) or smaller amygdala volumes, findings that appeared variable in adolescents from 12 to 21 years old depending on age, severity of trauma, and level of alcohol consumption (Phillips et al., 2021). In addition, our MRI findings paralleled those of a recent large study reporting smaller orbitofrontal volumes in adults with DSM-IV-TR bipolar-I disorder, schizophrenia-spectrum disorder, and in healthy controls who self-reported experiences of sexual, physical, and emotional abuse, and physical and emotional neglect (Begemann et al., 2023). Our data also supported recent findings of supplemental motor volume deficits that were associated with childhood maltreatment from a whole-brain coordinate-based meta-analysis of 45 prior studies (Yang et al., 2023). Our study extends brain volumetric findings to cohorts with AUD, HIV, and AUD+HIV comorbidity.

The second hypothesis proposed that cognitive and motor testing would reveal greater deficits in adults with AUD, HIV, and AUD+HIV comorbidity with a history of childhood abuse compared to counterparts without a history of childhood trauma. This hypothesis was partially supported in that childhood abuse history was associated with slower motor speed. A recent study found that in adults with early life adversity, particularly sexual abuse, slower speeded abilities were associated with epigenetic age acceleration measured from peripheral blood (Felt et al., 2023). We further found that verbal and visual learning was poorer in non-AUD groups (HIV and control groups) with a history of childhood abuse compared to counterparts without abuse, whereas in AUD groups (AUD and AUD+HIV) with and without childhood abuse, verbal and visual learning performance was statistically similar, and significantly poorer than controls without abuse history. A previous study examining early life stressors predictive of major depressive disorder in adulthood (emotional abuse, sexual abuse, and severe family conflict) found that these stressors predicted poorer processing speed and working memory performance compared to those not reporting these stressors; however, the same study found smaller orbitofrontal cortical volumes related to these stressors (Saleh et al., 2017), comporting with findings reported herein.

In this study of community members recruited for their AUD and HIV infection status, childhood trauma history was not a basis for recruitment into the study. Upon analyzing the childhood trauma data retrospectively, we found that the incidence of abuse reportedly experienced by participants was high. Among the clinical groups (AUD, HIV, and AUD+HIV), 46% reported experiencing sexual abuse, including rape or molestation during childhood, while 57% reported experiencing some form of physical abuse. The rate of witnessing one's mother or a close female relative being physically or emotionally abused was strikingly high among our cohort, ranging from 42 to 61% among groups experiencing childhood abuse. Even among our control sample, abuse incidence was high and is aligned with recent high estimates of abuse rates of the general population (Center for Disease Control and Prevention Fast Facts: Preventing Child Abuse and Neglect, 6 April 2022; https://www.cdc.gov/violenceprevention/childabuseandneglect/fastfact.html). Furthermore, rates of abuse reported indicated that abuse was largely continuous rather than indicated as isolated events. This pattern suggested that abuse spanned developmental phases during childhood and was a chronic condition for many; however, only a small proportion of our sample (~3%) had a formal diagnosis of post-traumatic stress disorder (PTSD), indicating that those reporting a history of abuse were not specifically reporting clinical levels of anxiety symptomatology related to their trauma history. Thus, it remains unclear and complex how trauma exacts effects on the brain, likely producing differential effects on the brain based on timing or duration of exposure (Lupien et al., 2009) or by causing adaptive modifications and alternate pathways during development (Teicher et al., 2003).

This study had several limitations. Like most studies of adults with early childhood trauma, we relied on retrospective interviews and self-report to procure information on childhood abuse history. Considering that participants with a history of AUD or HIV might also have imperfect recall and even memory deficits, one might question the validity of the reported trauma history, particularly whether participants have false memories or recall bias related to current emotional distress. Despite this possibility, adults who report traumas typically do not overreport their experiences (Shaffer et al., 2008; Williams, 1994). Further, the nature, severity, and high chronicity of the experiences reported in this study comport with findings that the most severe experiences can be identified by retrospective methods (Shaffer et al., 2008). Additionally, a small number of our participants who did not experience childhood abuse had a lifetime diagnosis of PTSD due to other types of trauma. Statistics recalculated with these participants' data omitted did not change the pattern of findings. Nonetheless, it does leave one to wonder how other trauma not examined here (for instance, divorce, neglect, loss of a parent) may have influenced brain and behavioral development and findings, especially given recent findings that individuals who have been abused were found to be neurobiologically and clinically distinct from those who were not abused (Teicher et al., 2022).

By having a hypothesis-driven approach, we chose selective brain regions based on the literature, thus preserving statistical power. Therefore, we may have overlooked other relationships that might be yielded by whole brain analyses.

Further limitations arise from the tenuousness of some of the observed brain volume deficits and poorer cognitive and motor performance correlations and group differences related to history of childhood trauma. Marginal differences could be due to the restricted sample sizes. That recognized, these results should not be dismissed, as these are adults who denied significant PTSD symptoms and are relatively functional suggesting that sequelae of abuse in adulthood be considered as a spectrum disorder, which would characterize the results of childhood trauma on a continuum. Results herein provide evidence of neurological, cognitive, and motor sequelae that are enduring across the lifespan and may produce a liability with aging into senescence in those with AUD, HIV, and AUD+HIV comorbidity. The restricted sample size does limit more detailed analyses. For instance, we are unable to determine whether specific brain and behavioral abnormalities are associated with particular trauma type, although our results comport with findings that cortical volume deficits are common to all maltreatment types (Cassiers et al., 2018). Further, the restricted sample sizes precluded examination of sex differences and other factors such as critical developmental periods that could aid in explaining previously conflicting findings with subcortical, particularly hippocampal volumes (Andersen et al., 2008). Despite limitations of sample size, the data available for the current analysis was adequate to reveal a dissociation of brain-functional relations distinguishing AUD with from those without childhood abuse history. Specifically, in the AUD group with an abuse history, poorer learning performance correlated with smaller orbitofrontal volumes but not frontal superior volumes, whereas the AUD group without an abuse history showed the opposite set of relations.

5. Conclusion

Our data suggest that childhood abuse is associated with brain and behavior sequelae in AUD, HIV, AUD+HIV comorbidity, and in those without either disease, that are observable and persistent in adulthood. Sequelae were notably present even in absence of salient psychological symptoms or formal diagnosis, further suggesting that childhood trauma

with its implications for stress responses be viewed as a "spectrum disorder." Given the high prevalence of abuse in people with AUD and in people with HIV infection, the results presented herein revealed substantial detrimental effects of abuse history as important contributors to brain and behavior deficits in these clinical groups and warrant attention in future research. The consequences of childhood abuse create substantial social, economic, and health burden. Indeed, childhood maltreatment has been considered the most preventable risk factor for psychiatric disorders (Teicher et al., 2022). Less than a decade ago, childhood abuse was considered an unappreciated confound in psychiatric neuroimaging studies (Teicher and Samson, 2016). This tradition remains pervasive (van der Kolk, 2016), in that childhood trauma continues to be an underdiagnosed phenomenon with lifelong ramifications deserving rigorous study and clinical attention.

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CRediT authorship contribution statement

Stephanie A. Sassoon: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Rosemary Fama:** Data curation, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Kilian M. Pohl:** Data curation, Investigation, Project administration, Resources, Writing – review & editing. **Adolf Pfefferbaum:** Data curation, Investigation, Project administration, Resources, Supervision, Writing – review & editing. **Edith V. Sullivan:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2024.100608.

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