Effect of HIV and Interpersonal Trauma on Cortical Thickness, Cognition, and Daily Functioning

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Background: Interpersonal trauma (IPT) is highly prevalent among HIV-positive (HIV+) individuals, but its relationship with brain morphology and function is poorly understood.

Setting: This cross-sectional analysis evaluated the associations of IPT with cognitive task performance, daily functioning, magnetic resonance imaging (MRI) brain cortical thickness, and bilateral volumes of 4 selected basal ganglia regions in a US-based cohort of aviremic HIV+ individuals, with (HIV+ IPT+) and without IPT exposure (HIV+ IPT−), and sociodemographically matched HIV-negative controls with (HIV− IPT+) and without IPT exposure (HIV− IPT−).

Methods: Enrollees completed brain MRI scans, a semistructured psychiatric interview, a neurocognitive battery, and 3 measures of daily functioning. Demographic and clinical characteristics of the 4 groups were described, and pairwise between-group comparisons performed using χ^2 tests, analysis of variance, or *t*-tests. Linear or Poisson regressions evaluated relationships between group status and the outcomes of interest, in 6 pairwise comparisons, using Bonferroni correction for statistical significance.

Results: Among 187 participants (mean age 50.0 years, 63% male, 64% non-white), 102 were HIV+ IPT+, 35 were HIV+ IPT−, 26 were HIV− IPT−, and 24 were HIV− IPT+. Compared with the remaining 3 groups, the HIV+ IPT+ group had more activities of daily living declines, higher number of impaired Patient's Assessment of Own Functioning Inventory scores, and lower cortical thickness in multiple cerebral regions. Attention/working memory test performances were significantly better in HIV− IPT− compared with the HIV+ IPT+ and HIV+ IPT− groups. Basal ganglia MRI volumes were not significantly different in any between-group comparisons.

Conclusion: IPT exposure and HIV infection have a synergistic effect on daily functioning and cortical thickness in aviremic HIV+ individuals.

Key Words: basal ganglia, cortical thickness, daily functioning, interpersonal trauma, HAND, HIV

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INTRODUCTION

The experience of interpersonal trauma (IPT), defined as a "deliberate threat or injury in the context of an interpersonal interaction,"[1] is highly prevalent among HIV-positive (HIV+) individuals. Evidence suggests high prevalence of intimate partner violence (55.3%), and childhood physical (39.3%) and sexual (42.7%) abuse among HIV+ women,[2] and sexual (35.2%) and physical (53.9%) abuse in HIV+ men.[3] IPT exposure is associated with poor HIV care outcomes, including increased risk of antiretroviral therapy (ART) failure,[4] AIDS-defining conditions,[5] AIDS-related morbidity and mortality,[6,7] health care utilization,[7] and poor engagement in HIV care.[8,9]

Although IPT exposure is associated with detrimental effects on HIV care outcomes, its effects on neurocognition and brain morphometry in HIV+ individuals are poorly understood. Studies suggest a synergistic effect of early life stress (a proxy for childhood trauma) and chronic HIV infection on magnetic resonance imaging (MRI) volumes of the corpus callosum, right anterior cingulate cortex, bilateral caudate, hippocampus, putamen,[10] and amygdala,[11] as well as performance on verbal fluency,[12] psychomotor, and

processing speed tasks.[11] Yet, because of the exclusive focus of these studies on childhood trauma, we cannot extrapolate their findings to HIV+ survivors of IPT in general. The cited studies are also limited by strict exclusion criteria[11] and uneven distribution of demographic factors between the HIV+ and HIV-negative cohorts.[10,12] The significant percentages of HIV+ participants with uncontrolled HIV viremia or not on ART[10–12] may have led to confounding effects of ongoing viral replication.

Finally, studies of cortical thickness in trauma-exposed individuals have consistently reported significant effects of trauma and/or post-traumatic stress disorder on prefrontal cortex and anterior cingulate cortex,[13,14] but this has not been evaluated in HIV+ populations. One previous study has reported reduced regional cortical thickness (ie, orbitofrontal, cingulate, primary motor and sensory cortex, temporal and frontal lobes) in aviremic HIV+ individuals,[15] but the study did not account for the effect of IPT.

This article reports on the results of a cross-sectional analysis of the associations of IPT exposure on cognitive task performance, daily functioning, MRI brain cortical thickness, and MRI volumes of 4 basal ganglia (BG) regions (amygdala, hippocampus, caudate, and putamen), in a US-based cohort of aviremic, ART-treated, HIV+ individuals, with (HIV+ IPT+) and without history of IPT exposure (HIV+ IPT−), and sociodemographically matched HIV-negative controls with (HIV− IPT+) and without IPT exposure (HIV− IPT−.

METHODS

Participants were recruited through an ongoing study at the NIH Clinical Center, which evaluates the natural course of neurocognitive outcomes in HIV+ individuals and sociodemographically matched controls. The Institutional Review Board of the National Institute of Allergy and Infectious Diseases approved the study (IRB# 13-N-0149). Written informed consent was obtained from all participants. Eligible participants were 18–65 years old, had at least a seventh-grade educational level by self-report, and could speak, read, and understand English language at the time of screening protocol consent and neuropsychological evaluation. Exclusion criteria were a history of central nervous system infection, other condition associated with cognitive impairment (eg, untreated sleep apnea), a history of head injury with loss of consciousness >30 minutes, current substance abuse that would impede participation in study procedures or interpretation of results, or severe psychiatric illness. Participants taking psychotropic medications were eligible if on a stable treatment regimen for ≥6 months. All participants underwent a screening assessment including a detailed history and physical examination, a blood draw for safety and research studies, and a semistructured psychiatric interview, the Client Diagnostic Questionnaire (CDQ), a validated screening tool for assessing psychiatric disorders in primary care settings, developed specifically for assessing the current mental health functioning and substance and alcohol abuse in HIV-affected populations.[16]

Eligibility criteria for the present data analysis included having completed the CDQ, neurocognitive tests and assessments of daily functioning, and brain MRI. Eligible HIV+ participants had to be on ART and aviremic (HIV viral load <40 copies/mL, allowing a one-time blip <300 copies/mL) for ≥1 year at the time of evaluation.

Assessment of IPT History

The CDQ was administered at intake visit by or under the supervision of a board-certified psychiatrist. Trauma history was assessed with the CDQ trauma inventory, which enquires about 13 types of trauma the participants may have experienced in their lives. Participants were classified as "IPT+" if they experienced one of the following: childhood physical or sexual abuse, intimate partner violence as an adult, physical, or sexual assault as an adult, direct combat, seeing people harming one another in the family as a child, or losing a child to death.

Assessment of Cognitive Task Performance

All participants were administered a comprehensive neuropsychological battery by a board-certified clinical neuropsychologist or trained psychometrist, assessing these cognitive domains: attention/working memory, executive functioning, information processing, verbal fluency, learning, psychomotor, and memory. Domain T-scores were obtained by averaging within domain demographically (age, sex, race/ethnicity, and education) corrected T-scores per administered tests. Antinori et al[17] criteria were used to determine HIV-associated neurocognitive disorder (HAND) diagnostic categories (no HAND, asymptomatic neurocognitive impairment, mild neurocognitive disorder, and HIV-associated dementia). For the purpose of the present analysis, which included cognitive test results from HIV-negative individuals, we replaced the term "HAND" with the HIV-neutral term "neurocognitive impairment" (NCI).

Assessment of Daily Functioning

The following measures of daily functioning were collected: (1) the Texas Functional Living Scale (TFLS), a performance-based measure assessing daily activity areas such as time, money/calculation, communication, and memory, yielding an overall T-score across areas[18]; (2) the Patient's Assessment of Own Functioning Inventory (PAO-FI), a self-report measure assessing daily functioning across memory, language and communication, etc, activities. Using a 6-point rating system, responses are scored as "impaired" if difficulty is reported as occurring "fairly often," "very often," or "almost always"[19]; and (3) the Activities of Daily Living (ADL) forms, a self-report measure assessing independent ability between "best" and "now" time points (responses are scored as "impaired" if there is a decline from "best" to "now").[20,21]

Imaging and Assessment of BG Volumes and Cortical Thickness

All participants underwent MRI scan on a 3T Philips Achieva scanner (Philips Medical Systems, Best, the

Netherlands) with an 8-channel head coil. The examination included T1-weighted MRI (3D MPRAGE, TR = 7 ms, TE = 3.2 ms, TI = 900 ms, FA = 9°, acquisition matrix of 240 × 240, 180 sagittal slice encoding, for a total acquisition time) of the brain, acquired at 1-mm isotropic resolution for structural imaging, along with other scans. Volumetric and cortical thickness information was extracted using FreeSurfer (https://surfer.nmr.mgh.harvard.edu) and tabulated. FreeSurfer segmentation outputs were inspected for labeling and segmentation errors. Volumes of individual structures from the left and right hemispheres were treated separately but were normalized to estimated total intracranial volume for further analysis.

This analysis focused on the bilateral MRI volumes of 4 BG regions previously reported as altered in HIV+ individuals with history of early life stress (amygdala, hippocampus, caudate, and putamen).[11,12] The thickness of the cerebral cortex was averaged across the entire brain (yielding measurements of global cortical thickness), as well as over 34 individual cortical regions bilaterally, for exploratory analysis. The following cortical regions were used for this analysis: banks of superior temporal sulcus, caudal anterior cingulate, caudal middle frontal, cuneus, entorhinal, frontal pole, fusiform, inferior parietal, inferior temporal, insula, isthmus cingulate, lateral occipital, lateral orbitofrontal, lingual, medial orbitofrontal, middle temporal, paracentral, parahippocampal, pars opercularis of inferior frontal gyrus, pars orbitalis, pars triangularis, pericalcarine, postcentral, posterior cingulate, precentral, precuneus, rostral anterior cingulate, rostral middle frontal, superior frontal, superior parietal, superior temporal, supramarginal, temporal pole, and transverse temporal.

Statistical Methods

Demographic characteristics were described using mean and SD or number and percent, by group. Between-group comparisons were performed using χ^2 tests or analysis of variance (or *t*-tests in the case of only 2 groups).

We then investigated differences in the measures of cognitive task performance. These comparisons were not adjusted for the demographics because the T-scores are already demographically corrected. Results were described using mean and SD for each group. After fitting the unadjusted global regression model, 6 pairwise comparisons were performed between groups, for each outcome.

To compare the measures of daily functioning between the groups, the results were described using mean and SD, and the models adjusted for sex, age, race, and education. Linear models were fit for TFLS. Poisson regression was fit for ADL and PAOFI. Six pairwise between-group comparisons were conducted, for TFLS, IADL, and PAOFI scores, respectively.

To compare brain MRI volumes, the results were described using mean and SD for each group. After fitting a global regression model, 6 comparisons were performed between groups, for each region. Models were first adjusted for sex, age, and race. A sensitivity analysis was conducted adjusting for history of being treated for drug abuse, and psychiatric medication prescription use in the last 6 months. The sensitivity analysis did not change the analysis results, so it is not reported in the results.

To evaluate differences in cortical thicknesses, the results were described using mean and SD for each group. After fitting a global regression model, 6 comparisons were performed between groups, for each region. Models were first adjusted for sex, age, and race. In addition, the models were adjusted for Wechsler Test of Adult Reading (WTAR) scores, (a measure of "crystallized intelligence" used as proxy for premorbid cognitive functioning), due to reported association with cortical thickness in several brain regions in neurologically intact adults.[22] A sensitivity analysis was conducted adjusting for history of being treated for drug abuse and psychiatric medication prescription use in the last 6 months. The sensitivity analysis did change the analysis results, so it is reported in the Results.

After reviewing the results of the comparisons listed above, we made a post hoc decision to evaluate if the regional cortical thicknesses that were significantly different between the groups predicted the PAOFI, IADL, or attention/working memory scores. Poisson regressions were used, adjusting for group status, age, gender, race, and education.

Statistical analysis was performed using R version 3.5.0. Statistical significance was set at $P < 0.05$. For each set of 6 pairwise between-group comparisons of outcomes of interest, including the comparisons of cognitive task performance, Bonferroni corrections were used to minimize chance of false discovery.

RESULTS

Participant Characteristics

There were 187 participants (102 HIV+ IPT+, 35 HIV+ IPT−, 26 HIV− IPT, and 24 IPT+ HIV−) who met the eligibility criteria and were included in this analysis. Table 1 shows the distributions of sociodemographic and clinical characteristics of all 187 participants, including HIV clinical characteristics for the 2 HIV+ groups. The mean participant age was 50.0 (SD = 8.8) years. Most participants were male (63%), black non-Hispanic (64%), and heterosexual (58%). The HIV+ IPT− group was 94% male, which was significantly different from the remaining 3 groups. Distributions of sexual orientation ($P = 0.01$) and gender ($P = 0.001$) differed significantly across groups. The mean time since HIV diagnosis was significantly longer for the HIV+ IPT+ group (17.9 years; SD = 9.0) relative to the HIV+ IPT− group (14.1; SD = 9.7) ($P = 0.048$) (Table 1).

Cognitive Task Performance

In the Bonferroni-corrected models, the HIV− IPT− group had significantly higher mean WTAR score (108.1; SD = 15.5) compared with the HIV+ IPT+ group (95.9; SD = 17.2). The HIV− IPT− group also had significantly better attention/working memory performance (53.6;

TABLE 1. Participants Characteristics by Group Status and Overall (n = 187)

	HIV− IPT− (n = 26)	HIV− IPT+ (n = 24)	HIV+ IPT− (n = 35)	HIV+ IPT+ (n = 102)	*P*	Overall (n = 187)
Demographic characteristics						
Age (M ± SD)	48.1 (9.6)	48.3 (9.4)	50.7 (8.0)	50.6 (8.7)	0.44	50.0 (8.8)
Gender (% male)	65%	33%	94%	58%	<0.001	63%
Education*						
Less than high school	0%	17%	14%	25%	0.11	18%
High school degree	12%	35%	14%	21%		20%
Some college	38%	17%	31%	25%		27%
College degree	15%	13%	17%	15%		15%
Advanced degree	35%	17%	23%	15%		19%
Race/ethnicity						
Non-hispanic white	58%	21%	34%	33%	0.29	35%
Non-hispanic black	42%	75%	57%	59%		58%
Hispanic white	0%	4%	6%	2%		3%
Hispanic black	0%	0%	0%	0%		0%
Asian	0%	0%	3%	2%		2%
Indian	0%	0%	0%	0%		0%
Other	0%	0%	0%	4%		2%
Sexual orientation†						
Heterosexual	88%	88%	33%	52%	0.01	58%
Gay/lesbian	12%	8%	64%	35%		33%
Bisexual	0%	4%	3%	6%		4%
Other	0%	0%	0%	7%		4%
Psychiatric characteristics						
Noninterpersonal trauma	46%	83%	49%	89%	<0.001	75%
Any trauma	46%	100%	49%	100%	<0.001	83%
Ever treated for drug abuse	0%	25%	20%	35%	<0.001	26%
PTSD¶	0%	17%	3%	35%	<0.001	22%
Psychotropic medication prescription in last 6 months‡	8%	29%	20%	42%	0.002	32%
Taking psych medications currently‡	8%	29%	20%	42%	0.002	32%
Depression¶	0%	0%	0%	10%	0.046	5%
BDI total score (M ± SD)	2.2 (2.4)	6.8 (7.9)	7.2 (6.4)	10.5 (8.3)	<0.001	8.2 (7.9)
HIV clinical characteristics						
Years since HIV diagnosis (M ± SD)			14.1 (9.7)	17.9 (9.0)	0.048	16.9 (9.3)
Years on antiretroviral therapy (ART) (M ± SD)			9.3 (11.2)	8.6 (7.8)	0.26	10.7 (8.1)
Years from diagnosis to ART (M ± SD)			4.9 (8.0)	6.5 (8.3)	0.31	6.1 (8.2)
Nadir CD4 (M ± SD)			217.9 (169.1)	201.5 (177.5)	0.63	205.7 (174.9)
Ever on zidovudine (AZT)§			24%	24%	1	24%
Ever on efavirenz§			44%	47%	0.83	46%
Ever on a d-drug§			16%	16%	1	16%
Hepatitis C coinfection‖			9%	23%	0.13	19%

Only 12 regions significantly different in HIV− IPT− vs. HIV + IPT+ are shown. Cortical thicknesses for each region were averaged between left and right hemispheres; Banks STS = "banks of superior temporal sulcus" (ie, cortical areas around superior temporal sulcus).

*2 participants with missing data (1 in HIV− IPT− and 1 in HIV− IPT+ group).

†6 with missing data (2 in HIV− IPT+; 1 in HIV+ IPT−; and 3 in HIV+ IPT+).

‡6 with missing data (2 in HIV-IPT-; 1 in HIV+IPT-; and 3 in HIV + IPT+).

§18 with missing data (8 in HIV+/IPT+ and 10 in HIV+/IPT−).

‖1 participant from HIV+ IPT− group with missing data.

¶The 2 CDQ depressive syndromes (major and minor depressive syndrome) were grouped as "depressive syndrome".

BDI, Beck Depression Inventory; d-drugs, dideoxynucleoside analogues; PTSD, post-traumatic stress disorder.

SD = 7.5) compared with the HIV+ IPT+ (48.3; SD = 7.9) and HIV+ IPT− (47.4; SD = 6.5) groups (both $P = 0.002$) (see Figure 1, Supplemetal Digital Content, http://links.lww.com/QAI/B457). There were no significant differences between the groups on any of the remaining 6 cognitive domains, overall average T-scores, GDS, or prevalence of NCI (see Table 1, Supplemetal Digital Content, http://links.lww.com/QAI/B457).

Daily Functioning

The HIV+ IPT+ group had significantly more ADL declines and "impaired" PAOFI scores compared with the remaining 3 groups. In the Bonferroni-corrected adjusted models, the mean number of IADL declines in the IPT+ HIV+ group was 1.40 (SD = 2.11), which was significantly more than in the HIV+ IPT− (0.52; 1.09; $P < 0.001$), HIV− IPT+ (0.38; 0.67; $P = 0.003$), and HIV− IPT− (0.58; SD = 0.83; $P = 0.005$) groups. The mean number of "impaired" PAOFI scores in the IPT+ HIV+ group was 5.84 (SD = 6.87), which was significantly higher than in the HIV+ IPT− (2.69; SD = 5.57; $P < 0.001$), HIV− IPT+ (2.36; SD = 3.71; $P < 0.001$), and HIV− IPT− (0.75; SD = 0.90; $P < 0.001$) groups. In addition, HIV− IPT− had significantly less "impaired" PAOFI scores compared with the HIV− IPT+ ($P = 0.003$) and HIV+ IPT− ($P < 0.001$) groups. The TFLS T-scores did not differ between the 4 groups (Table 2).

Brain MRI Volumes

There were no significant differences between the groups on any of the MRI BG volumes (see Table 2, Supplemetal Digital Content, http://links.lww.com/QAI/B457).

Cortical Thickness

In the Bonferroni-corrected models adjusting for sex, age, race, WTAR score, history of drug abuse, and psychiatric medication prescription in the last 6 months, there were multiple differences on the measures of MRI brain cortical thickness between the HIV+ IPT+ and HIV− IPT− groups, and some differences between the HIV+ IPT− and HIV− IPT− groups and between the HIV− IPT− and HIV− IPT+ groups. The HIV+ IPT+ group had significantly lower mean cortical thickness relative to the HIV− IPT− group in the following 12 regions: banks of superior temporal sulcus ($P = 0.02$), caudal middle frontal ($P = 0.009$), cuneus ($P = 0.003$), inferior parietal ($P = 0.007$), lateral orbitofrontal ($P = 0.03$), pars opercularis ($P = 0.01$), pericalcarine ($P = 0.002$), precentral ($P = 0.02$), precuneus ($P = 0.02$), rostral middle frontal ($P = 0.01$), superior frontal ($P = 0.008$), and superior parietal ($P = 0.04$). The HIV+ IPT+ group also had significantly lower mean overall cortical thickness relative to the HIV− IPT− group ($P = 0.01$). The HIV+ IPT− group had significantly lower cortical mean thickness relative to the HIV− IPT− group in the following 3 regions: banks of superior temporal sulcus (0.01), inferior parietal ($P = 0.008$), and medial orbitofrontal ($P = 0.03$). Finally, the HIV-IPT+ group had significantly lower mean cortical mean thickness relative to the HIV− IPT− group in the pericalcarine region ($P = 0.005$). There were no significant differences in cortical thicknesses between the HIV+ IPT− and HIV− IPT+ groups, between the HIV+ IPT− and HIV− IPT+ groups, or between the HIV+ IPT+ and HIV+ IPT− groups. Table 3 summarizes the significant differences in averaged regional and global cortical thicknesses. Figure 1 shows mean averaged cortical thicknesses of 12 regions that were significantly different between the HIV− IPT− and HIV+ IPT+ groups. The complete results for left and right hemisphere and for bilateral averaged cortical thicknesses are shown in Tables 3 and 4, Supplemetal Digital Contents, http://links.lww.com/QAI/B457.

TABLE 2. Daily Functioning Outcomes by HIV/IPT Group Status

	HIV− IPT− (n = 26)	HIV− IPT+ (n = 24)	HIV+ IPT− (n = 35)	HIV+ IPT+ (n = 102)	*P*, Adjusted*
TFLS: Overall T-score	53.4 ± 10.1	52.8 ± 10.6	50.5 ± 9.8	49.3 ± 11.2	HIV− IPT− vs HIV+ IPT+: 1.0
					HIV− IPT− vs HIV+ IPT−: 1.0
					HIV− IPT− vs HIV− IPT+: 0.26
					HIV− IPT+ vs HIV+ IPT+: 0.16
					HIV− IPT+ vs HIV+ IPT−: 0.17
					HIV+ IPT− vs HIV+ IPT+: 1.0
ADL declines	0.58 ± 0.83	0.38 ± 0.67	0.52 ± 1.09	1.40 ± 2.11	HIV− IPT− vs HIV+ IPT+: 0.005
					HIV− IPT− vs HIV+ IPT−: 1.0
					HIV− IPT− vs HIV− IPT+: 1.0
					HIV− IPT+ vs HIV+ IPT+: 0.003
					HIV− IPT+ vs HIV+ IPT−: 1.0
					HIV+ IPT− vs HIV+ IPT+: <0.001
PAOFI: No. of impaired scores	0.75 ± 0.90	2.36 ± 3.71	2.69 ± 5.57	5.84 ± 6.87	HIV− IPT− vs HIV+ IPT+: <0.001
					HIV− IPT− vs HIV+ IPT−: <0.001
					HIV− IPT− vs HIV− IPT+: 0.003
					HIV− IPT+ vs HIV+ IPT+: <0.001
					HIV− IPT+ vs HIV+ IPT−: 1.0
					HIV+ IPT− vs HIV+ IPT+: <0.001

*6 *P*-values for each row, one for each pairwise comparison between groups, all Bonferroni adjusted. ADL and PAOFI were used Poisson regression for count data. Models were adjusted for sex, age, race, and education.

ADL, activities of daily living; PAOFI, patient's assessment of own functioning inventory; TFLS, Texas Functional Living Scale.

TABLE 3. Average Cortical Thickness Differences Between IPT/HIV Groups*

Cortical Region	HIV− IPT− vs HIV+ IPT+	HIV− IPT− vs HIV+ IPT−	HIV− IPT− vs HIV− IPT+	HIV− IPT+ vs HIV+ IPT+	HIV− IPT+ vs HIV+ IPT−	HIV+ IPT− vs HIV+ IPT+
Banks STS	0.129 (0.044); 0.02	0.152 (0.05); 0.01	0.134 (0.054); 0.09	−0.005 (0.042); 1	0.018 (0.051); 1	0.129 (0.044); 0.02
Caudal middle frontal	0.145 (0.045); 0.009	0.096 (0.051); 0.36	0.107 (0.055); 0.34	0.039 (0.043); 1	−0.011 (0.053); 1	0.145 (0.045); 0.009
Cuneus	0.133 (0.037); 0.003	0.112 (0.042); 0.05	0.121 (0.046); 0.06	0.012 (0.036); 1	−0.009 (0.044); 1	0.133 (0.037); 0.003
Inferior parietal	0.144 (0.049); 0.007	0.162 (0.055); 0.008	0.113 (0.06); 0.23	0.031 (0.047); 1	0.049 (0.057); 1	0.144 (0.049); 0.007
Lateral orbitofrontal	0.117 (0.047); 0.03	0.083 (0.054); 0.49	0.087 (0.059); 0.56	0.03 (0.046); 1	−0.004 (0.056); 1	0.117 (0.047); 0.03
Mean cortical thickness	0.113 (0.065); 0.01	0.097 (0.073); 0.1	0.093 (0.08); 0.22	0.02 (0.062); 1	0.004 (0.076); 1	0.113 (0.065); 0.01
Medial orbitofrontal	0.105 (0.051); 0.17	0.151 (0.058); 0.03	0.129 (0.063); 0.18	−0.023 (0.05); 1	0.022 (0.06); 1	0.105 (0.051); 0.17
Pars opercularis	0.119 (0.038); 0.1	0.026 (0.043); 1	0.069 (0.047); 1	0.05 (0.037); 1	−0.042 (0.045); 1	0.119 (0.038); 0.1
Pericalcarine	0.125 (0.044); 0.002	0.068 (0.049); 0.46	0.143 (0.054); 0.005	−0.018 (0.042); 1	−0.075 (0.051); 0.36	0.125 (0.044); 0.002
Precentral	0.129 (0.043); 0.02	0.086 (0.049); 0.5	0.12 (0.054); 0.17	0.009 (0.042); 1	−0.034 (0.051); 1	0.129 (0.043); 0.02
Precuneus	0.131 (0.052); 0.02	0.112 (0.058); 0.16	0.108 (0.064); 0.3	0.023 (0.05); 1	0.004 (0.06); 1	0.131 (0.052); 0.02
Rostral middle frontal	0.137 (0.049); 0.01	0.108 (0.055); 0.17	0.117 (0.06); 0.19	0.02 (0.047); 1	−0.009 (0.057); 1	0.137 (0.049); 0.01
Superior frontal	0.167 (0.041); 0.008	0.137 (0.047); 0.12	0.108 (0.051); 0.56	0.06 (0.04); 1	0.029 (0.048); 1	0.167 (0.041); 0.008
Superior parietal	0.126 (0.071); 0.04	0.108 (0.08); 0.24	0.127 (0.088); 0.17	−0.001 (0.069); 1	−0.019 (0.083); 1	0.126 (0.071); 0.04

*Adjusted first for sex, age, WTAR, and race. Then also adjusted for ever treated for drug abuse and psych med prescription in the last 6 months. Results shown are mean (SE); *P*-value. *P*-value is for the group difference (Bonferroni adjusted for 6 comparisons). Group difference is provided as group 1 minus group 2. Side-specific results provided in Table 3, Supplemental Digital Content, http://links.lww.com/QAI/B457. The comparisons for brain regions, which had no significant results, are not shown; full table provided in Table 4, Supplemental Digital Content, http://links.lww.com/QAI/B457.

Banks STS = "banks of superior temporal sulcus" (ie, cortical areas around superior temporal sulcus).

Associations of Cortical Thickness With PAOFI, ADL, and Attention/Working Memory

Among the 13 cortical regions that were significantly different between groups, 12 were associated with attention/working memory, 11 were associated with PAOFI, and 3 were associated with IADL scores. The mean overall cortical thickness was also associated with both attention/working memory and PAOFI (Table 4).

DISCUSSION

This cross-sectional analysis evaluated the effects of IPT and chronic, ART-treated virologically suppressed HIV infection on cognitive task performance, daily functioning, cerebral cortical thickness, and selected BG regions. IPT survivors constituted most HIV+ participants in the cohort, highlighting the need for NeuroHIV studies to elucidate the role of IPT even among virally suppressed HIV+ individuals. The significant effect of HIV+ IPT+ group status on cortical thickness in brain regions observed in this study, in light of sporadic and inconsistent effects of either HIV+ or IPT+ status alone, suggests primarily a combined effect of IPT and HIV infection. This effect remained significant after controlling for the WTAR score, suggesting that it should not be attributed solely to factors predating HIV infection. We also observed a significant effect of HIV+ status on attention/working memory, regardless of IPT status. The regional cortical thicknesses, which were significantly different by IPT and/or HIV status, showed significant associations with attention/working memory, PAOFI, and/or IADL scores.

This study is the first to report a combined effect of HIV and IPT on cortical thickness. This combined effect goes beyond that previously observed with either exposure alone, as it includes the precuneus, and the regions of primary visual cortex (ie, cuneus and pericalcarine cortex). This finding is important because it implies the need to account for the effect of IPT to fully understand the risk and underlying mechanisms of NeuroHIV.

The mechanisms whereby HIV and IPT affect cortical thickness remain to be elucidated in future research. Traumatic events may lead to altered glucocorticoid secretion resulting in hypocortisolemia or hypercortisolemia, resulting in changes in glucocorticoid sensitivity in peripheral leukocytes, changes in peripheral lymphocyte subsets, and chronic low-grade inflammation, which is characterized by increased plasma levels of TNF-α, IL-1β, IL-6, and C -reactive protein.[23] HIV infection in a virologically suppressed patient is also characterized by sustained chronic inflammation and elevated cytokines, including IL-6, CD14, CD163, TNFR1, TNFR2, IL2RA, KYN/TRP, and d-Dimer, which are associated with increased risk of non-AIDS adverse events, including cardiovascular, respiratory, gastrointestinal, and immune pathology.[24,25] We have previously reported significant associations between post-traumatic stress disorder (one potential consequence of IPT) and markers of inflammation and immune activation in HIV+ individuals with controlled viremia, including higher percentages of memory CD8 T-cells, lower percentages of naïve CD8 T-cells, and higher rates of C -reactive protein >3 mg/L.[26] The excess of circulating cytokines observed in both chronic conditions could hypothetically combine to cause cortical atrophy, possibly directly through chemokine interference with monoamine metabolism[23] or with synaptic transmission,[27] or indirectly (eg, through systemic vascular or immune pathology).[23]

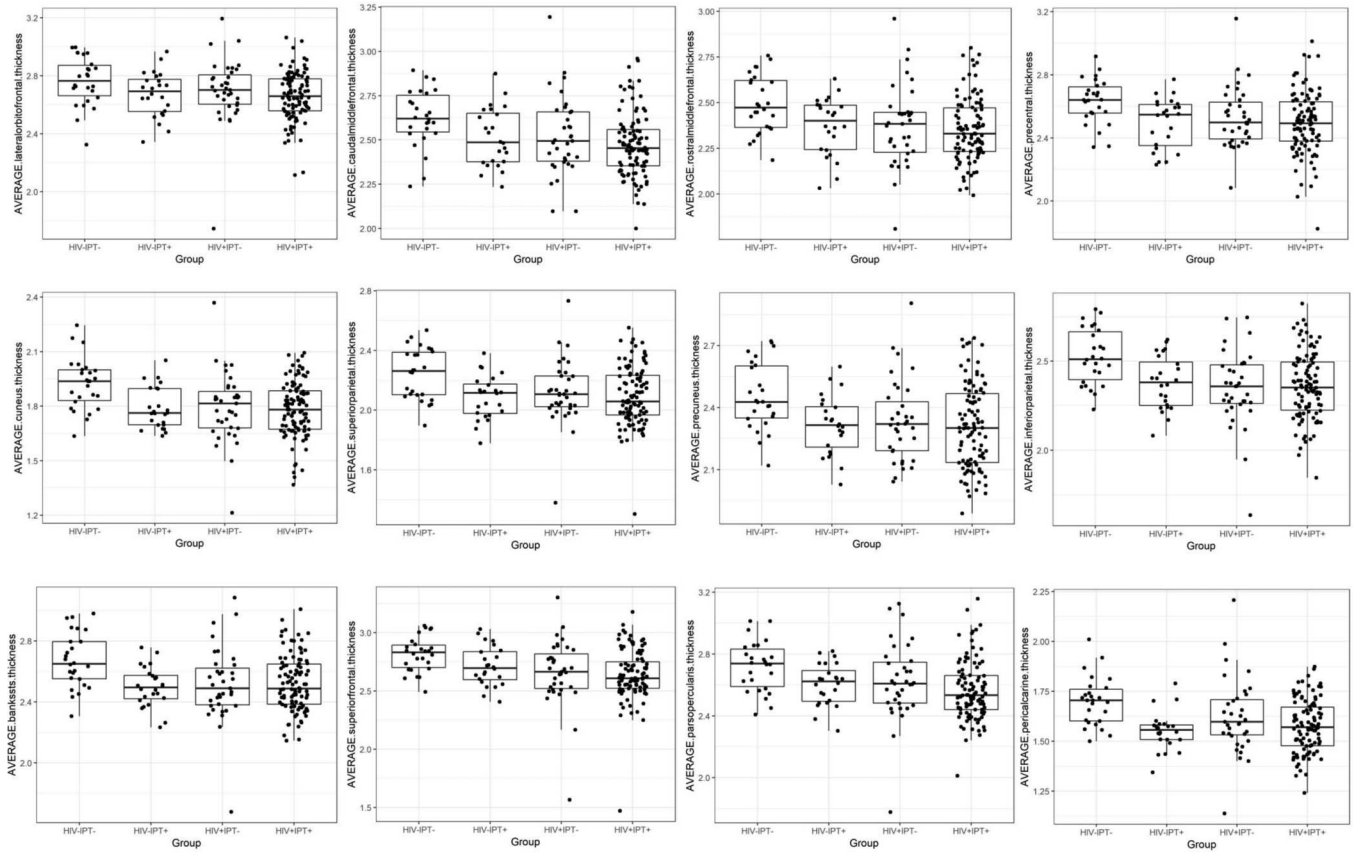

FIGURE 1. Mean cortical thickness between groups adjusted for sex, age, WTAR, and race.

The observed combined effect of HIV and IPT on 2 measures of daily functioning (ie, IADL and PAOFI) is another significant finding of this study. The measures of daily functioning were used in the context of the comprehensive neuropsychological battery, to indicate level of functional impairment associated with neurocognitive deficits. Given the absence of observed combined HIV/IPT effect on the neuropsychological domains, it is possible that IADL

TABLE 4. Associations Between Brain Regions That Significantly Differ Between IPT/HIV Groups and PAOFI, IADL, and Attention/Working Memory Scores

Region	PAOFI	IADL	Attention/Working Memory
Banks STS	−0.12 (0.21); 0.58	−0.09 (0.45); 0.84	10.56 (3.34); 0.002
Caudal middle frontal	−0.51 (0.22); 0.02	−0.77 (0.45); 0.09	8.27 (3.36); 0.01
Cuneus	−0.86 (0.25); <0.001	−0.74 (0.51); 0.15	9.18 (4.01); 0.02
Inferior parietal	−0.75 (0.21); <0.001	−0.92 (0.44); 0.03	9.92 (3.38); 0.004
Lateral orbitofrontal	−1.06 (0.19); <0.001	−1.03 (0.42); 0.01	7.21 (3.51); 0.04
Mean cortical thickness	−0.98 (0.25); <0.001	−1.16 (0.52); 0.02	12.94 (4.11); 0.002
Medial orbitofrontal	−0.78 (0.19); <0.001	−0.91 (0.41); 0.03	6.94 (3.21); 0.03
Pars opercularis	−0.33 (0.21); 0.11	−0.43 (0.43); 0.31	7.9 (3.28); 0.02
Pericalcarine	1.21 (0.27); <0.001	−0.33 (0.58); 0.56	6.02 (4.54); 0.19
Precentral	−0.61 (0.21); 0.003	−0.44 (0.42); 0.30	6.95 (3.45); 0.05
Precuneus	−0.61 (0.21); 0.004	−0.68 (0.43); 0.11	7.18 (3.35); 0.03
Rostral middle frontal	−0.76 (0.23); <0.001	−0.76 (0.47); 0.11	8.42 (3.46); 0.02
Superior frontal	−1.04 (0.16); <0.001	−0.62 (0.32); 0.05	9.5 (2.87); 0.001
Superior parietal	−0.72 (0.2); <0.001	−0.53 (0.39); 0.18	7.99 (3.24); 0.01

Poisson regressions adjusted for group, age, gender, race, and education. Results shown are mean (SE); *P*-value. *P*-values are for the main effect of region on PAOFI, IADL, or attention/working memory.

Banks STS = "banks of superior temporal sulcus" (ie, cortical areas around superior temporal sulcus).

and PAOFI are more sensitive to the combined IPT/HIV effect in a virally suppressed cohort such as this one. Alternatively, it is possible that factors other than the neurocognitive domains are affecting the daily functioning in HIV+ survivors of IPT. The standard neurocognitive battery used in this and other NeuroHIV studies is not designed to capture psychological symptoms that are salient to survivors of IPT (eg, dissociative symptoms) and are known predictors of detrimental health outcomes.[28,29] Given the high prevalence of IPT among HIV+ individuals, future NeuroHIV studies should consider systematic inclusion of measures designed to capture those symptoms, such as Trauma Symptom Inventory[30] and Multiscale Dissociation Inventory.[31]

Another important finding of this study was the significant effect of HIV+ status on attention/working memory, regardless of IPT status. This may indicate that attention/working memory is primarily affected through HIV-specific mechanisms.

The 12 regional cortical thicknesses that were significantly different by IPT/HIV status showed significant associations with attention/working memory, PAOFI, and/or IADL results, even after adjusting for HIV/IPT group status, age, gender, race, and education. The roles of these 12 regions range from basic visual processing (cuneus) to complex executive tasks including behavioral, memory, and emotional regulation (eg, superior parietal and rostral middle frontal). Based on these associations, one can hypothesize that effects of HIV and IPT combine to affect cortical thickness, which in turn leads to impairment of daily functioning. This hypothesis could be tested in future longitudinal studies. Functional neuroimaging studies could be used to identify more specific linkages between the affected cortical regions and specific tasks of daily functioning.

Unlike previous studies of childhood trauma in virally nonsuppressed cohorts,[10,11] there was no significant effect of IPT and/or HIV status on MRI brain volumes of caudate, putamen, hippocampus, and amygdala, in this study. The effect of trauma on BG may be specific to childhood trauma, rather than IPT in general. Alternatively, this negative finding could potentially suggest a neuroprotective effect of sustained virological suppression on BG.

This study has limitations. With the cross-sectional design, we can only hypothesize about causation and direction of the observed significant effects. We elected not to focus on evaluating effect of specific individual types of trauma (eg, sexual trauma only or childhood trauma only) because of the high prevalence of wide array of trauma exposures in the overall cohort (see Table 5, Supplemental Digital Content, http://links.lww.com/QAI/B457), which would likely have significant confounding effect. Instead, we chose the more inclusive construct of IPT, which is already established in the trauma literature as predictor of poor health outcomes.[32] In the longitudinal phase of this ongoing study, we plan to delineate specific types of IPT and determine mediators of the observed IPT effect. Although all HIV+ participants in this analysis were virologically suppressed, most of them have been living with HIV for a long time (some since early 1990s), and their overall low nadir CD4 counts suggest high likelihood of a significant residual effect of chronic HIV disease. Ideally, a study of this type would focus on HIV+ individuals who started ART and achieved aviremia soon after acquisition of HIV, which would further minimize any potential legacy effect of past years of untreated and chronic HIV disease. This study did not include measures of stigma. HIV stigma could have had significant additional traumatic effect in the HIV+ participants, especially those living with HIV since the 1990s, that could have had additional traumatic effect not specifically captured by the CDQ trauma inventory.

In conclusion, in this US-based cohort of HIV+ individuals, we not only observed a high prevalence of IPT, but also a significant combined effect of chronic HIV disease and IPT on daily functioning and cortical thickness despite viral suppression. We also observed independent effect of HIV on attention/working memory, regardless of IPT history. These results suggest that IPT exposure is associated with increased risk of NeuroHIV complications even among aviremic HIV+ individuals on ART, in addition to that of chronic HIV disease alone. Longitudinal and mechanistic studies are indicated to further elucidate the direction, causality, clinical implications, and underlying pathophysiology of the observed effect.

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