Archival Report

Biological Psychiatry: CNNI

Accelerated and Premature Aging Characterizing Regional Cortical Volume Loss in Human Immunodeficiency Virus Infection: Contributions From Alcohol, Substance Use, and Hepatitis C Coinfection

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ABSTRACT

BACKGROUND: Life expectancy of successfully treated human immunodeficiency virus (HIV)–infected individuals is approaching normal longevity. The growing HIV population ≥50 years of age is now at risk of developing HIV-associated neurocognitive disorder, acquiring coinfection with the hepatitis C virus (HCV), and engaging in hazardous drinking or drug consumption that can adversely affect trajectories of the healthy aging of brain structures.

METHODS: This cross-sectional/longitudinal study quantified regional brain volumes from 1101 magnetic resonance imaging scans collected over 14 years in 549 participants (25 to 75 years of age): 68 HIV-infected individuals without alcohol dependence, 60 HIV-infected individuals with alcohol dependence, 222 alcohol-dependent individuals, and 199 control subjects. We tested 1) whether localized brain regions in HIV-infected individuals exhibited accelerated aging, or alternatively, nonaccelerated premature aging deficits; and 2) the extent to which alcohol or substance dependence or HCV coinfection altered brain aging trajectories.

RESULTS: The HIV-infected cohort exhibited steeper declining volume trajectories than control subjects, consistently in the frontal cortex. Nonaccelerated volume deficits occurred in the temporal, parietal, insular, and cingulate regions of all three diagnostic groups. Alcohol and drug dependence comorbidities and HCV coinfection exacerbated HIV-related volume deficits. Accelerated age interactions in frontal and posterior parietal volumes endured in HIV-infected individuals free of alcohol or substance dependence and HCV infection comorbidities. Functionally, poorer HIV-associated neurocognitive disorder scores and Veterans Aging Cohort Study indices correlated with smaller regional brain volumes in the HIV-infected individuals without alcohol dependence and alcohol-dependent groups.

CONCLUSIONS: HIV infection itself may confer a heightened risk of accelerated brain aging, potentially exacerbated by HCV coinfection and substance dependency. Confirmation would require a prospective study with a preinfection baseline.

Keywords: Aging, Alcohol dependence, Brain, Hepatitis C, HIV, MRI

https://doi.org/10.1016/j.bpsc.2018.06.006

Before antiretroviral therapy (ART) was introduced in the mid-1990s, individuals infected with human immunodeficiency virus (HIV), whether young or old, lived for only 10 to 12 years after diagnosis. Currently, life expectancy estimates of ART-treated individuals, even when infected with HIV as young adults, are 64 years of age for men and 62 years of age for women, and are approaching longevity of the HIV-negative U.S. population—77 years of age for men and 82 years of age for women. Despite the effectiveness of ART, HIV infection continues to have major public health and clinical ramifications. In the United States, nearly half of the 1.2 million people living with HIV are 50 years of age and older (1). As many as 40% of HIV-infected individuals 55 years of age and older had late-stage infection at the time of diagnoses (2), are at highest risk for premature cognitive decline, and are more likely to delay treatment initiation, thereby jeopardizing optimal outcomes (3,4). With advancing age, commonly acquired HIV comorbidities that can curtail life quality or expectancy include misuse of alcohol or other substances (occurring in approximately 75%) (5) or dependence on alcohol or other substances (~33%) (6) and coinfection with hepatitis C virus (HCV) (7) [in ~25%) (8)].

In HIV infection, cross-sectional studies report greater brain gray matter than white matter volume deficits accompanying

ISSN: 2451-9022

Table 1. Demographics of the Four Study Groups at Most Recent Visit[a]

	Control Group (C)		Alc-Only Group (A)		HIV-only Group (H)		HIV + Alc Group (HA)		
	Value	*n*	Value	*n*	Value	*n*	Value	*n*	Group Differences
Male/Female		107/92		156/66		47/21		38/22	$\chi^2 = 13.4$, $p = .004$
Age, Years	48.3 (14.1), [25.1–75.0]	199	49.3 (10.1), [25.4–70.1]	222	54.4 (9.1), [25.5–69.6]	68	54.5 (7.1), [32.9–68.9]	60	C = A < H = HA
Education, Years	16.0 (2.3)	146	13.4 (2.4)	213	13.5 (2.4)	66	13.0 (2.1)	58	C > A = H = HA
Socioeconomic Status[b]	25.5 (11.6)	193	40.9 (14.4)	221	40.7 (14.2)	68	45.2 (12.2)	60	C < A = H = HA
Body Mass Index, kg/m^2	25.9 (4.2)	128	26.8 (4.8)	158	26.6 (4.7)	65	26.8 (4.9)	55	NS
Self-defined Ethnicity									$\chi^2 = 97.80$, $p < .0001$
Asian, *n*	28		4		0		0		
African American, *n*	28		71		31		38		
Caucasian, *n*	127		117		34		17		
Other/unknown, *n*	16		30		3		5		
HIV Onset Age, Years	—		—		35.3 (9.6)	66	35.2 (7.7)	60	NS
Range, years					16.1–54.5		19.1–54.4		
Length of HIV Infection, Years	—		—		19.4 (7.9), [2.9–40.0]	66	19.1 (7.6), [2.9–35.1]	60	NS
CD4 Count (at Final Observation)	—		—		655.5 [18–1576]	64	567 [25–1318]	57	NS
CD4 Count <200 Ever (Yes/No)					21/47		30/30		$\chi^2 = 4.861$, $p < .028$
Viral Load, HIV Copies/mL	—		—		26 [U to 111,800]	50	38 [U to 225,747]	49	NS
HCV Infection (Yes/No)[c]	0/89	89	37/115	152	23/43	66	31/28	59	$\chi^2 = 57.2$, $p < .001$
VACS Score	13.7 (11.6), [0–59]	87	16.2 (12.9), [0–52]	145	29.7 (19.1), [0–81]	58	31.1 (16.9), [5–77]	48	C = A; C < H = HA
AIDS-Defining Event (Yes/No)[d]	—		—		26/40		35/25		$\chi^2 = 4.514$, $p = .034$
Blood Chemistry Panel									
Prealbumin, mg/dL	29.9 (6.7)	75	27.7 (7.8)	119	27.3 (8.5)	62	26.4 (8.6)	55	C > A = H = HA
Creatinine, mg/dL	79.3 (32.5)	43	85.0 (30.1)	75	106.9 (61.7)	45	97.5 (95.1)	34	C < H
eGFR, mL/min/1.73 m^2	85.7 (14.2)	37	85.7 (13.4)	58	72.3 (25.6)	37	75.4 (23.1)	25	C > H
AST, U/L	20.6 (5.5)	89	27.6 (25.0)	147	31.0 (27.3)	66	34.1 (20.3)	58	C < A = H = HA
ALT, U/L	21.5 (10.7)	89	31.0 (53.2)	147	28.1 (20.8)	66	32.0 (24.4)	58	C < A = H = HA
Hemoglobin, g/dL	133.6 (34.4)	88	126.7 (43.2)	146	125.0 (44.5)	65	127.2 (38.6)	57	NS
Platelets, thousand/uL	246.3 (66.6)	88	236.4 (57.1)	145	204.2 (59.6)	65	227.3 (62.5)	57	C = A = HA > H
Hematocrit, %	403.6 (105.2)	88	397.4 (108.8)	146	388.5 (119.4)	65	396.6 (96.1)	57	NS
Alcohol Diagnosis Onset Age, Years	—		25.5 (9.6)	222	—		23.5 (9.3)	60	NS
Total Alcohol Consumed, kg	34.0 (57.0)	130	1202.0 (885.8)	222	86.5 (95.7)	68	1081.2 (916.2)	60	C < H < A = HA
Alcohol Consumed in the Past Year, kg	—		32.5 (40.9)	221	—		10.6 (15.3)	60	A > HA
Days Since Last Drink	—		109 [1–5127]	222	—		30 [0–7863]	60	NS
Nonalcohol Drug Dependence (Yes/No)	0/199	199	128/94	222	29/39	68	46/14	60	$\chi^2 = 199.0$, $p < .0001$
Cocaine (dependent/nondependent)	—		86/136	222	22/46	68	37/23	60	$\chi^2 = 13.1$, $p = .0014$
Amphetamine (dependent/nondependent)	—		44/178	222	8/60	68	15/45	60	$\chi^2 = 3.8$, $p = .151$
Opiate (dependent/nondependent)	—		30/192	222	5/63	68	18/42	60	$\chi^2 = 14.0$, $p = .0009$
Cannabis (dependent/nondependent)	—		50/172	222	7/61	68	16/44	60	$\chi^2 = 6.2$, $p = .045$
Nicotine (dependent/nondependent)	12/101	113	129/59	188	30/34	64	36/19	55	$\chi^2 = 9.8$, $p = .007$
Cigarette smoker (never/current + past)	108/7 + 6	121	59/98 + 36	193	33/18 + 13	64	19/29 + 10	58	$\chi^2 = 106.4$, $p < .0001$
NART IQ or WTAR FSIQ[e]	105.6 (9.3)	130	98.2 (11.4)	191	95.3 (12.3)	67	93.4 (11.9)	60	C > A = H = HA

Table 1. Continued

	Control Group (C)		Alc-Only Group (A)		HIV-only Group (H)		HIV + Alc Group (HA)		
	Value	*n*	Value	*n*	Value	*n*	Value	*n*	Group Differences
HAND Category (0–3)	0 (0–1)	138	0 (0–3)	213	2 (0–3)	65	1 (0–3)	59	C < A = H = HA
Verbal/language	−0.09 (0.84)	73	−0.79 (0.99)	107	−1.01 (1.11)	64	−0.87 (0.96)	56	C > A = H = HA
Executive function	−0.07 (0.89)	83	−0.69 (1.15)	141	−0.96 (1.59)	64	−1.25 (1.52)	57	C > A = H = HA
Learning/memory	0.03 (0.84)	64	−0.93 (0.89)	111	−081 (0.98)	62	−1.11 (0.97)	55	C > A = H = HA
Speed of information processing	0.22 (0.72)	75	−0.38 (0.90)	126	−0.42 (0.84)	64	−0.69 (0.96)	57	C > A = H = HA
Motor skills	−0.12 (0.69)	73	−0.79 (0.93)	114	−0.99 (1.35)	63	−1.07 (1.51)	57	C > A = H = HA
Quality of social functioning	0.14 (0.76)	137	−1.96 (1.70)	213	−2.00 (1.55)	65	−2.45 (1.97)	58	C > A = H = HA

Values are mean (SD), median [range], or *n* unless otherwise indicated.

AIDS, acquired immunodeficiency syndrome; Alc, alcohol dependent; ALT, alanine aminotransferase; AST, aspartate transaminase; eGFR, estimated glomerular filtration rate; FSIQ, full-scale IQ; HAND, human immunodeficiency virus–associated neurocognitive disorder; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV + Alc, human immunodeficiency virus infected with alcohol dependence; NART, National Adult Reading Test; NS, not significant; U, undetectable viral load; WTAR, Wechsler Test of Adult Reading; VACS, Veterans Aging Cohort Study.

[a]Not all participants had all scores.

[b]Lower score indicates higher status.

[c]Includes only participants with serologically determined HCV status.

[d]An AIDS-defining event was defined as a CD4 count <200 or HIV-related opportunistic infection.

[e]Correction factor: 10 points added to NART IQ to make it comparable to the WTAR IQ.

advanced symptom stage (9). Gray matter volume in the frontal, parietal (10–12), cingulate, and motor cortices; thalamus; and hippocampi (13,14) is smaller relative to control subjects and has been associated with low CD4 cell count (15,16), even in virally suppressed HIV. That HIV infection can disrupt central nervous system integrity raises the likelihood that substance use comorbidities (17–20) and HCV coinfection (15,21) may compound central nervous system effects, increasing vulnerability to accelerated aging (22).

Mild to moderate cognitive deficits in HIV remain a problem, especially with extended longevity (23–26), despite the declining prevalence of HIV-associated dementia with combination ART (27). HIV-associated neurocognitive disorder (HAND) indices, assessed using comprehensive neuropsychological batteries (28), allow for grading of functional impairment (29,30), from asymptomatic neurocognitive impairment to HIV-associated dementia (31,32). Although the profile of impairment is heterogeneous (33,34), neuropsychological assessments of treatment-stabilized HIV patients often report a compromise in domains of attention, psychomotor speed, memory, and executive control (35,36), likely related to central nervous system compromise.

Identifying HIV-related factors promoting premature aging or accelerated normal aging trajectory of regional brain integrity requires longitudinal investigation using quantitative methods across a broad age span. The few available longitudinal magnetic resonance imaging (MRI) studies of HIV infection report either no evidence for age interactions in middle-aged to older virologically suppressed HIV groups in 2- to 2.5-year follow-up studies (37–40), or only modest evidence for HIV-age interactions targeting white matter (10,41,42). One of the longest controlled studies found accelerated volume decline over an average of 3.4 years in HIV-infected men 60 years of age and older in total cortical gray matter volume and in the frontal, caudate, cerebellar, and brain stem regions (43). In general, the length of follow-up has been relatively short, the sample sizes have been small, the age range has been restricted, and common comorbidities have more often been excluded or "controlled for" rather than examined directly.

To address these shortcomings, the current longitudinal analysis quantified regional brain volumes from 1101 MRI scans collected in 549 participants included in one of four groups: 68 HIV-infected individuals (HIV only), 60 HIV-infected individuals with alcohol dependence (HIV + Alc), 222 alcohol-dependent individuals (Alc only), and 199 control subjects. At the final MRI, most HIV participants were 50 years of age or older (73.5% HIV group; 78.3% HIV + Alc group), thereby enhancing the opportunity to answer questions regarding aging with HIV. Accordingly, this study focused on three main areas. First, we tested whether localized brain regions in HIV-infected individuals exhibited accelerated aging, which would be revealed by group-by-age interactions, where brain tissue volume deficits in the diagnostic groups would show faster declining trajectories with aging than in control subjects; alternatively, volume differences would reflect premature aging deficits if they proceeded in parallel, rather than interacting with the aging trajectories of the control subjects (22). Second, we examined correlates of regional volume deficits, including age, sex, alcohol and substance dependence comorbidity, and HCV coinfection. Third, we explored relations between brain

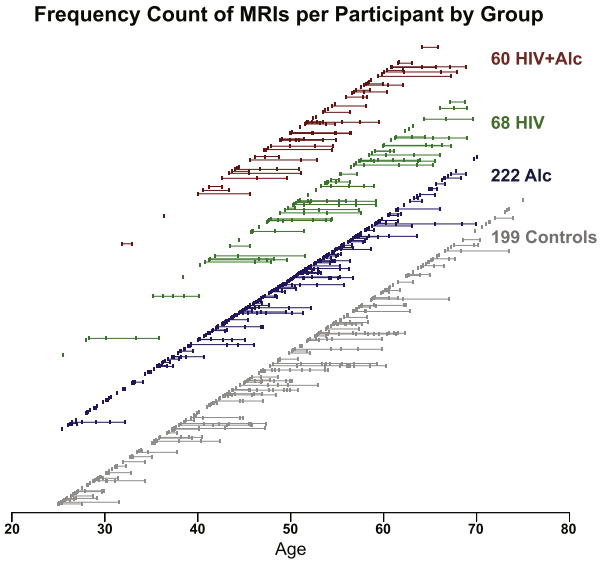
volumes and neuropsychological and physiological functions in the HIV-infected participants.

METHODS AND MATERIALS

Participants

The participants were drawn from ongoing cross-sectional and longitudinal MRI brain structural studies [control subjects (44), HIV-only group (14), HIV + Alc group (45), and Alc-only group (46)]. From those studies, we accrued an adequate longitudinal dataset to address the current study aims; accordingly, the aggregate of the data described herein is novel. Research clinicians administered the Structured Clinical Interview for DSM-IV (47) to all participants, who provided written informed consent to join the study, which was approved by the institutional review boards of SRI International and Stanford University School of Medicine.

The age range of each group at study entry was limited to 25 to 75 years (Table 1). Included were 1101 MRIs from men and women, most examined multiple times at 1-month to 8-year intervals: 417 acquired in 199 control subjects, 409 in 222 Alc individuals, 152 in 68 HIV-only individuals, and 123 in 60 HIV + Alc individuals. Of the 549 participants, 103 control subjects, 106 Alc individuals, 29 HIV-only individuals, and 22 HIV + Alc individuals had only one MRI; 96 control subjects, 116 Alc individuals, 39 HIV-only individuals, and 60 HIV + Alc individuals had two or more MRIs (Figure 1). Drug use history and serologically confirmed HCV status were determined in most participants.



MRIs	Control	Alc	HIV	HIV+Alc
1	103	106	29	22
2	47	71	12	20
3	21	31	15	12
4	11	9	7	5
5+	17	5	5	1
Total individuals=	199	222	68	60
Total number of MRIs =	417	409	152	123

Figure 1. Horizontal lines represent individual participants; dots represent each magnetic resonance imaging (MRI) scan per participant over time for all 549 participants and 1101 MRI sessions: control subjects (gray), alcohol-dependent individuals (Alc) (blue), human immunodeficiency virus (HIV)–infected individuals (green), and HIV-infected individuals with alcohol dependence (HIV + Alc) (red).

MRI Acquisition and Analysis

Structural T1-weighted inversion-recovery prepared spoiled gradient recalled MRI data were acquired between April 11, 2003, and March 3, 2017, on a 3T whole-body MR system (GE Healthcare, Waukesha, WI). Detailed acquisition parameters and analysis methods appear in the Supplement (46).

Despite the 14-year span of data acquisition, all MRI data were processed at once using a common procedure. Parcellated maps of gray matter defined six lobar regions: the frontal, temporal, parietal, occipital, cingulate, and insular cortices (Figure 2). All but the insula were further divided: the precentral, superior, orbital, middle, inferior, supplemental motor, and medial frontal cortices; superior, middle, and inferior temporal cortices; postcentral, superior, inferior, supramarginal, precuneus, and paracentral parietal cortices; calcarine, cuneus, lingual, and lateral occipital cortices; and anterior and middle posterior cingulate cortices. Subcortical areas quantified included hippocampus, parahippocampus, amygdala, caudate, putamen, pallidum, and thalamus for 30 regions included for evaluation (Figure 3). To reduce the number of comparisons and because we had no hypotheses regarding structural laterality, gray matter volumes of bilateral hemispheres were summed for each region and used as the metric for analysis.

HAND and Composite Scores

HAND is a categorical rating based on deviations from the means of composite scores representing six functional domains [cf., (28,30)]: executive function, learning/memory, verbal/language, speed of information processing, motor skills, and quality of social functioning. Raw test scores included in each composite score were age corrected based on laboratory control participants, and expressed as standardized *Z* scores. The HAND categorical score ranged from 0 to 3, where 0 indicated normal performance. Descriptions of each test and derivation of the summary HAND score appear in the Supplement.

Statistical Analysis

Statistical analyses were performed with R (version 3.2.4) (48) and were based on linear or quadratic mixed effects models (*lmer*), which incorporated cross-sectional and longitudinal brain observations, to test primary variables of diagnosis, age, and sex (see Supplement for complete description).

To adjust for the magnitude of regional cortical gray matter volumes, which is highly correlated with supratentorial volume, the regression of regional volume on supratentorial volume was computed for control subjects with a general linear model (*lm* in R) and then applied to the data of all participants at each scan. Only control data at the initial MRI were used in the fitting function to ensure that the estimate of relation was not influenced by disease or by differences in numbers of MRI data per subject used in the fitting function. This procedure minimized

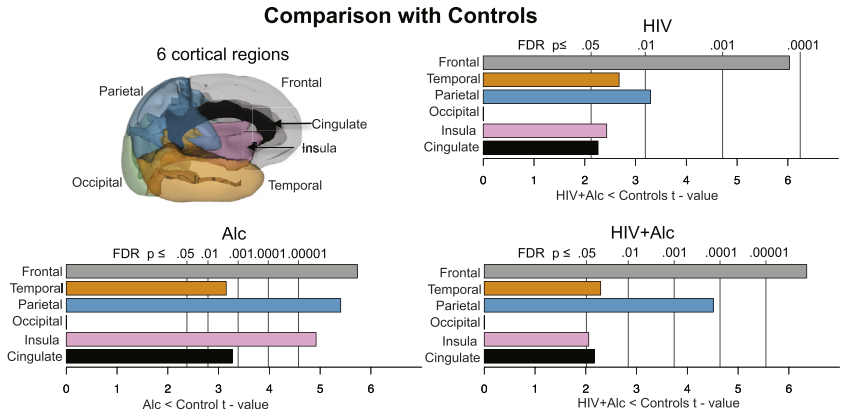


Figure 2. (Top panel) Sagittal view of a surface-rendered brain indicating the six global cortical regions used for volumetric analysis. The three lateral bar graphs show values from *t* tests for regional volumes indicating group differences and false discovery rate (FDR)–corrected *p* values. In five of the six regions, the three diagnostic groups had smaller volumes than the control group. Alc, alcohol-dependent individuals; HIV, human immunodeficiency virus–infected individuals; HIV + Alc, human immunodeficiency virus–infected individuals with alcohol dependence.

sex effects. The effect of age on brain volumes was computed (*lmer*) for all control subjects for all observations. Similarly, the results of this function were then used to compute age-independent observations for all participants regardless of diagnosis over all observations, enabling tests to examine aging effects in diagnostic groups over and above those effects observed in control subjects. We also computed the R^2 for the fixed (group) effects and fixed + random (group + individual variation) effects of the *lmer* for the main group differences between the control group and each diagnostic group and for group-by-age interactions and group-by-sex interactions (49) (Table 2 and Supplemental Table S1). R^2 provides estimates of effect sizes, where R^2 <.01 is trivial, >.01 to .09 is small to medium, >.09 to .25 is medium to large, and >.25 is large to very large.

Using the age- and sex-independent brain data for each diagnostic group separately, drug-dependent (cocaine, cannabis, amphetamine, opiates) and non–drug-dependent participants were tested against the 199 control subjects with a general linear model (*lm*) followed by analysis of variance (*anova*). The age- and sex-independent brain values were used to examine the influence of drinking, HIV, HCV, and neuropsychological variables with *t* tests for dichotomous variables and Pearson correlations for continuous variables.

RESULTS

Diagnostic Groups and Regional Brain Volumes

Of the six major cortical volumes examined, five regions showed volume deficits in the combined group of 128 participants with HIV (i.e., HIV-only and HIV + Alc groups) relative to the control group; the exception was the occipital lobe. The same deficit pattern was present in the HIV-only (n = 68), HIV + Alc (n = 60), and Alc-only (n = 222) groups (Figure 2, Table 2).

Analysis of 30 regions revealed common volume deficits in all three diagnostic groups relative to the control group in seven regions: five frontal (precentral, superior, middle, inferior, and medial), postcentral parietal, and thalamus (false discovery rate corrected) (Figure 3). Volume deficits common and unique to the combined alcoholic groups (HIV + Alc and Alc only) were the superior parietal, precuneus, middle temporal, and hippocampal regions. Deficits unique to the HIV + Alc group were in the orbital frontal cortex (Figure 3, Supplemental Table S1).

Accelerated Aging: Age-by-Diagnosis Interactions

The effect of age was examined independently for each group. The control subjects showed significant aging effects in five of the six cortical regions (all but the insula). A search for diagnosis-by-age interactions over and above those measured in the control subjects revealed evidence for accelerated aging (diagnosis-by-age interaction) solely in the frontal cortex for the total HIV, the HIV-only, and Alc-only groups, but not for the HIV + Alc group (Table 2, Figure 4).

Examination of the 30 subregions revealed diagnosis-by-age interactions in the superior frontal cortex of the total HIV, HIV-only, HIV + Alc, and Alc-only groups (Figure 5; Supplemental Table S1, green cells; Supplemental Figures S1 and S2). Interactions unique to the HIV-only group were the middle and medial frontal and postcentral parietal cortices (Figure 5), whereas age interactions with the midposterior cingulate and pallidal volumes were unique to the HIV + Alc group. The supplementary motor cortex showed age interactions in the HIV-only and HIV + Alc groups, whereas the precentral cortex showed age interactions in the HIV-only and Alc-only groups (Supplemental Table S1, green cells).

Premature Aging Differences: Deficits Without Age-by-Diagnosis Interactions

For the lobar regions, only the HIV + Alc group exhibited the premature aging effect, having a frontal volume deficit but no age interaction. Additional volume deficits without age interactions were found in several of the 30 regions for each diagnostic group (Supplemental Table S1, orange cells). Specifically, all three groups had volume deficits without age interactions in the frontal inferior cortex and thalamus. The HIV + Alc and Alc-only groups also had nonaccelerated deficits in the medial frontal and postcentral, superior, and parietal cortices; precuneus; and hippocampus. The HIV-only and Alc-only groups had deficits in superior temporal, parietal inferior, and insular cortices. The Alc-only group had uniquely nonaccelerated deficits in the frontal inferior, paracentral parietal, and midposterior cingulate cortices and the pallidum.

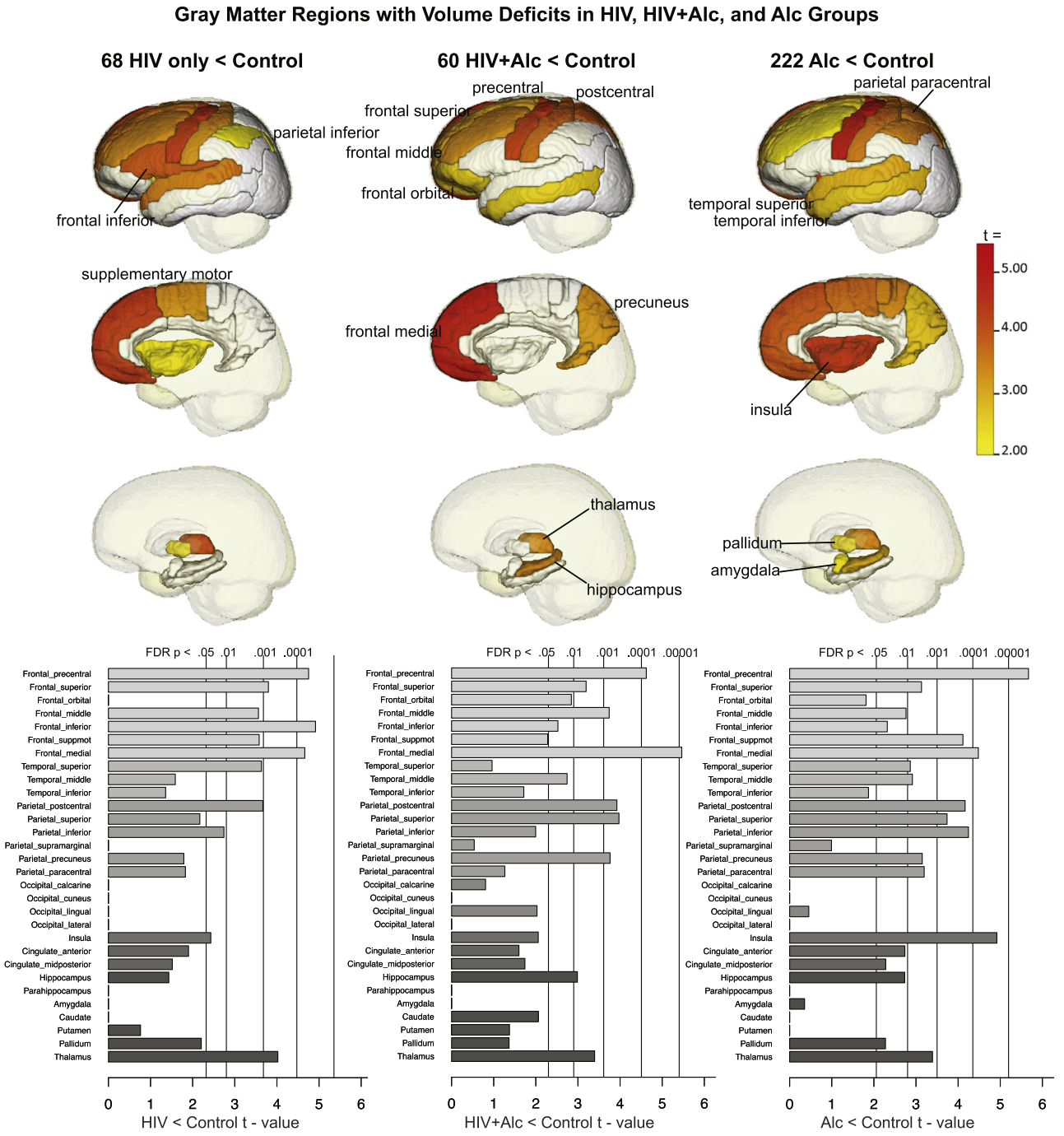


Figure 3. (Top panel) Lateral and two medial sagittal views of the gray matter regions showing volume deficits in each diagnostic group. (Bottom panel) Values from *t* tests for regional volumes indicating group differences and false discovery rate (FDR)–corrected *p* values, in which a diagnostic group had smaller volumes than the control group. Alc, alcohol-dependent individuals; HIV, human immunodeficiency virus–infected individuals; HIV + Alc, human immunodeficiency virus–infected individuals with alcohol dependence.

Sex-by-Diagnosis Interactions in Regional Brain Volumes

Testing for diagnosis-by-sex interactions yielded significant effects in only the HIV + Alc group. Three regional volumes indicated greater volume deficits in the male than in the female HIV + Alc participants (posterior central parietal [t = 2.048, p = .041], inferior parietal [t = 3.076, p = .002], and thalamus [t = 2.18, p = .029]). As with the lobar regions, age-sex effects were limited to the HIV + Alc group, which showed three modest interactions (postcentral parietal, inferior parietal, and thalamus volumes):

Table 2. Diagnosis and Age- or Sex-Interaction Effects (Two-Group* *Imer*) for Six Lobar Volumes

	Group Differences				Interactions								
			R^2				R^2				R^2		Best Fit
Region	*t*	FDR *p*	Fixed	Fixed + Random	Group by Age	FDR *p*	Fixed	Fixed + Random	Group by Sex	FDR *p*	Fixed	Fixed + Random	Age Function
199 Control Subjects vs. 128 Total HIV Individuals													
Frontal	−7.556	.000[a]	.385	.969	−3.037	.014[a]	.377	.970	0.330	.911	.202	.957	Linear
Temporal	−3.232	.002[a]	.192	.985	0.929	.476	.197	.986	−0.610	.911	.063	.978	Linear
Parietal	−4.864	.000[a]	.241	.979	0.173	.863	.241	.979	1.152	.911	.137	.970	Quadratic
Occipital	1.857	.063	.017	.964	1.320	.373	.022	.964	0.026	.979	.006	.965	Linear
Insula	−2.858	.006[a]	.031	.978	−0.847	.476	.030	.978	0.307	.911	.028	.979	Linear
Cingulate	−2.767	.007[a]	.052	.991	−2.137	.098	.049	.991	0.742	.911	.035	.990	Quadratic
199 Control Subjects vs. 68 HIV-Only Individuals													
Frontal	−6.029	.000[a]	.371	.971	−3.177	.009[a]	.364	.972	0.214	.941	.163	.960	Linear
Temporal	−2.677	.015[a]	.206	.988	0.513	.755	.209	.988	0.075	.941	.052	.980	Linear
Parietal	−3.294	.003[a]	.228	.979	0.424	.755	.230	.980	−0.115	.941	.088	.970	Quadratic
Occipital	2.554	.016	.031	.966	1.195	.465	.036	.965	0.297	.941	.018	.967	Linear
Insula	−2.431	.018[a]	.026	.978	−0.312	.755	.026	.978	0.920	.941	.026	.979	Linear
Cingulate	−2.262	.024[a]	.046	.991	−1.740	.246	.043	.991	0.454	.941	.028	.990	Quadratic
199 Control Subjects vs. 60 HIV + Alc Individuals													
Frontal	−6.352	.000[a]	.354	.972	−1.658	.292	.348	.972	0.354	.854	.170	.964	Linear
Temporal	−2.293	.044[a]	.180	.987	1.272	.325	.187	.987	−1.044	.854	.046	.981	Linear
Parietal	−4.512	.000[a]	.250	.982	−0.168	.867	.249	.982	2.079	.225	.149	.974	Quadratic
Occipital	0.285	.776	.014	.977	0.665	.607	.016	.977	−0.184	.854	.000	.979	Linear
Insula	−2.058	.048[a]	.020	.979	−1.236	.325	.020	.980	−0.516	.854	.020	.980	Linear
Cingulate	−2.168	.045[a]	.041	.992	−1.809	.292	.038	.992	0.652	.854	.027	.991	Quadratic
199 Control Subjects vs. 222 Alc-Only Individuals													
Frontal	−5.732	.000[a]	.279	.975	−3.019	.015[a]	.297	.975	−0.604	.778	.071	.973	Linear
Temporal	−3.151	.002[a]	.149	.985	1.778	.113	.148	.985	−0.249	.803	.026	.980	Linear
Parietal	−5.405	.000[a]	.191	.981	1.316	.226	.190	.982	−0.668	.778	.078	.976	Quadratic
Occipital	1.376	.169	.008	.983	2.090	.109	.011	.983	−0.537	.778	.004	.983	Linear
Insula	−4.920	.000[a]	.058	.983	−1.924	.109	.061	.983	0.901	.778	.055	.984	Linear
Cingulate	−3.272	.002[a]	.035	.992	0.231	.817	.035	.992	−0.456	.778	.025	.991	Quadratic

Effects were calculated in R software (two-group* lmer). R^2 provides estimates of effect sizes, where R^2 <.01 is trivial, >.01 to .09 is small to medium, >.09 to .25 is medium to large, and >.25 is large to very large.

Alc, alcohol dependent; FDR, false discovery rate; HIV, human immunodeficiency virus; HIV + Alc, human immunodeficiency virus–infected with alcohol dependence.

[a]Significant at $p \leq .05$, FDR corrected, in the expected direction.

while slightly faster in younger HIV + Alc women than in men, the overall rates of volume decline with aging were the same in HIV + Alc men and women.

Drug Dependence Comorbidity and Regional Brain Volumes

The effects of drug dependence on the Alc-only group appear elsewhere (46). Statistical testing for the effects of each drug of abuse separately was not possible in the HIV groups because of inadequate sample sizes. Thus, the primary diagnostic groups of HIV-only or HIV + Alc individuals were divided into drug-dependent (including any of one of the four drugs of abuse: cocaine, opiates, methamphetamine, or marijuana) and non–drug-dependent subgroups. Regardless of drug or alcohol history, the combined HIV group showed frontal volume deficits relative to control subjects. In addition, relative to the control group, the HIV-only drug-dependent group had volume deficits in parietal and temporal cortices, and the HIV + Alc drug-dependent group had volume deficits in the insular, cingulate, and parietal cortices (Table 3). Critically, the frontal volume deficit endured in the HIV group without a history of drug or alcohol dependence. Similarly, the frontal and parietal volume deficits endured in the HIV + Alc group without drug dependence (Table 3, Supplemental Figure S3).

HCV Coinfection and Regional Brain Volumes

We next examined the effects of HCV coinfection on volumes of the six lobar volumes in the combined HIV, HIV-only, and HIV + Alc groups against 89 control participants with known HCV serostatus (Table 4). HCV-positive versus HCV-negative status was also evaluated within each group. Participants in the combined HIV + HCV group had smaller volumes than

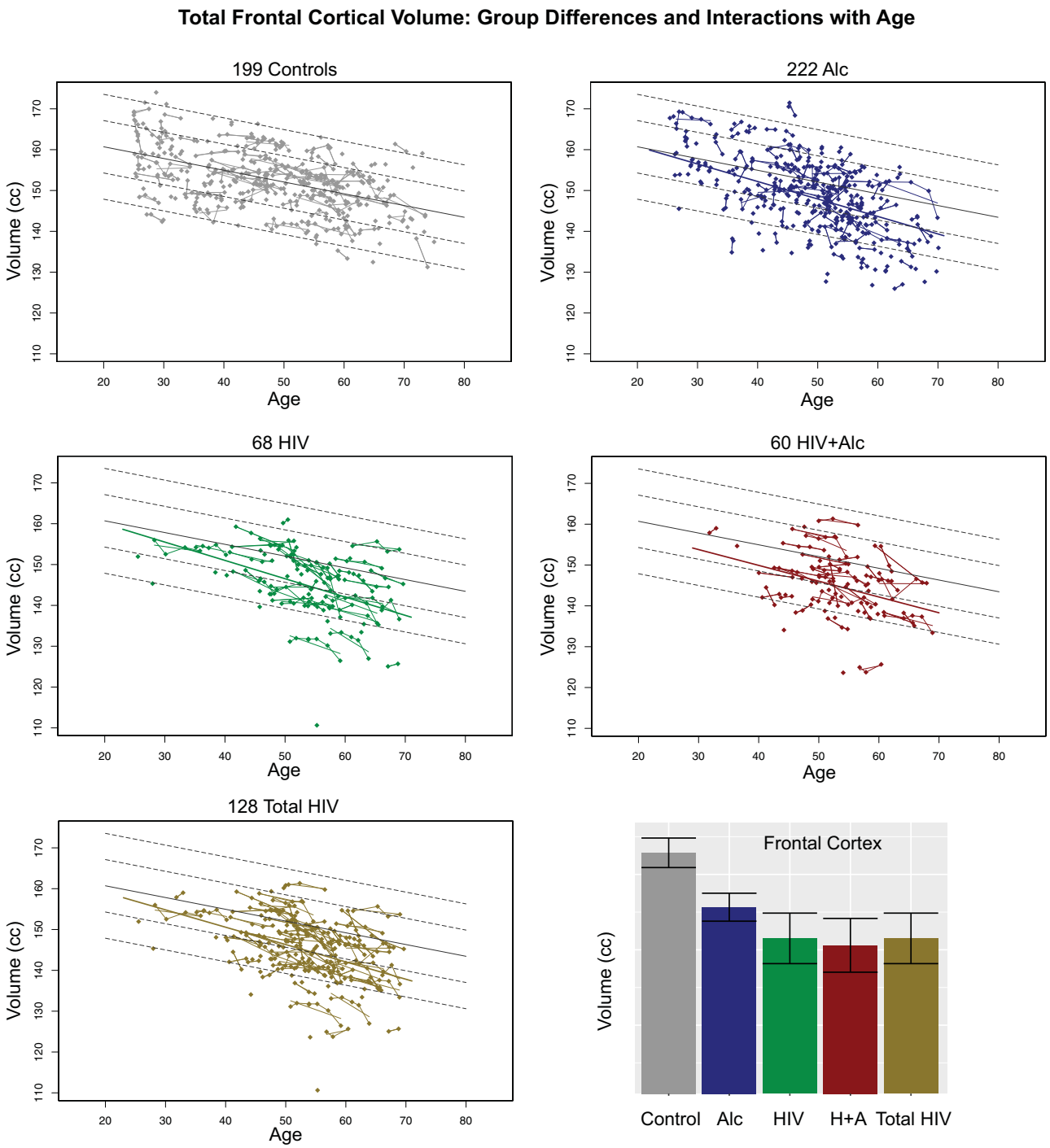


Figure 4. The control scatterplot shows volumes at each magnetic resonance imaging (MRI) of the 199 individual control subjects plotted on their mean (solid gray regression) ± 1 and 2 SD (dashed gray lines). The diagnostic group scatterplots show volumes at each MRI of each participant plotted on their mean regression (blue line for the alcohol-dependent individuals [Alc] group, green line for the human immunodeficiency virus–infected individuals [HIV] group, red line for the human immunodeficiency virus–infected individuals with alcohol dependence (HIV + Alc) group, and gold line for the total HIV group) and over-plotted on the control mean (solid gray regression) ± 1 and 2 SD (dashed gray lines).

control subjects in the frontal, temporal, parietal, insular, and cingulate cortices; however, volumes of these structures were not different between HCV-positive and HCV-negative HIV participants (Figure 5, Table 4). HIV-infected individuals, with or without HCV infection, exhibited frontal cortical volume deficits, although this deficit was at trend level in those without

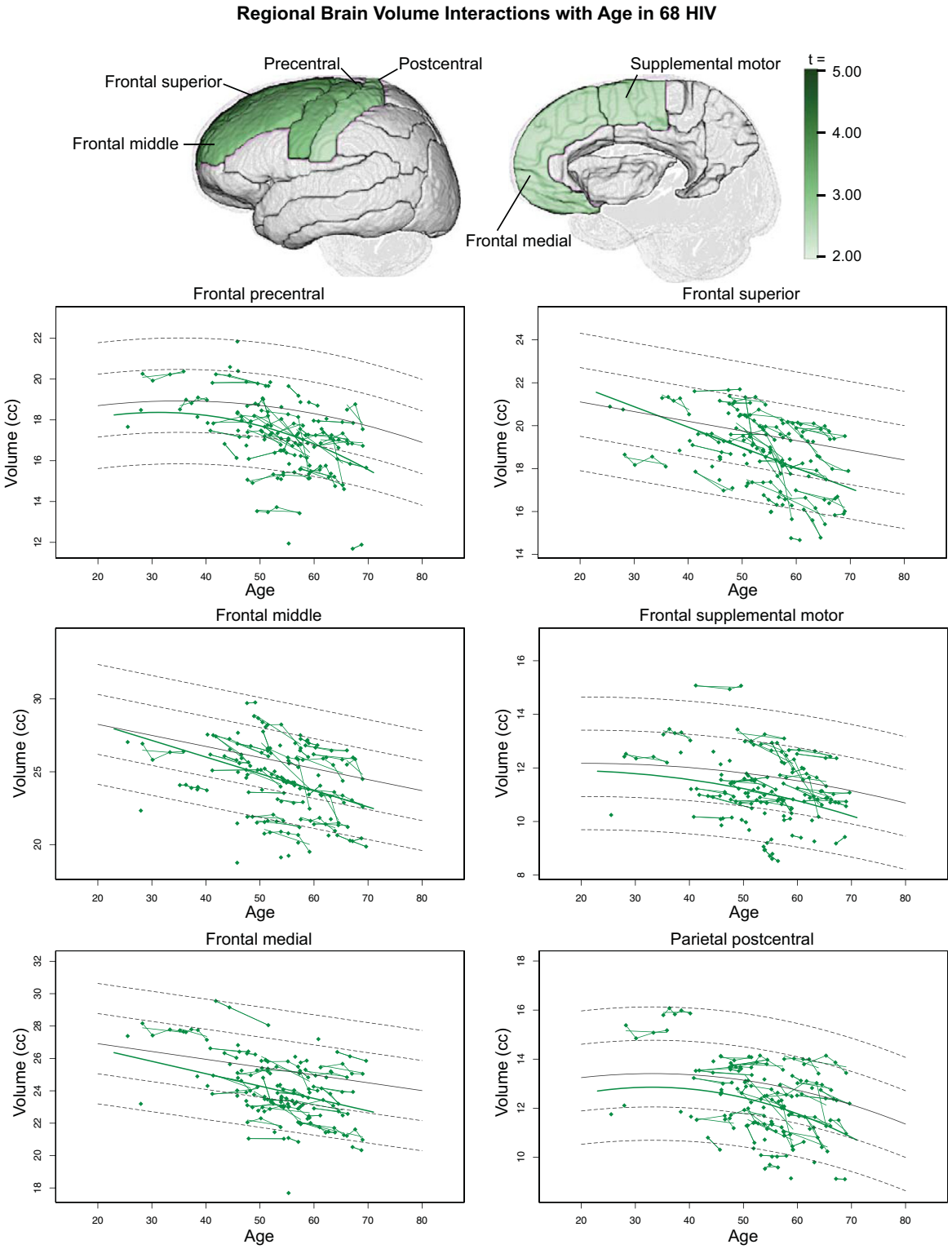


Figure 5. Color-coded brain regions and scatter plots of significant age-by-diagnosis interactions in the human immunodeficiency virus–infected individuals (HIV)–only group indicating age-related declines in excess of those detected in the control subjects (gray regression lines).

alcohol dependence or HCV infection. The most salient effect emerged in the HIV + Alc + HCV group, which had smaller frontal and temporal volumes than HIV + Alc individuals negative for HCV (Table 4, Supplemental Figure S4).

HIV Infection Absent Comorbidities and Regional Brain Volumes

This set of analyses examined whether regional volumes and age-HIV interactions endured in a subset of 24 HIV-infected participants with no history of drug or alcohol dependence or HCV infection. Significant volume deficits were detectable in the frontal superior cortex. Despite reduced power with the smaller sample size, HIV diagnosis-by-age interactions remained significant for the total frontal lobar volume and volumes of four frontal subregions (precentral, superior, middle, and medial) and the postcentral parietal cortex (Figure 6, Supplemental Table S2).

Exploratory Relations Between Clinical and Performance Indices and Brain Volumes

Analyses exploring relations between HIV-infection factors and regional brain volumes used data from the two HIV-infected groups combined. For lowest CD4 count known, the participants were divided into those with a count <200 and those that exceeded that limit. All MRI datasets with CD4 count data resulting in 265 data pairs were tested with *t* tests. Four of the six regions (frontal, cingulate, parietal, and temporal cortices) had small but significant correlations with CD4 count in the predicted direction (lower CD4 count with smaller volume) and met familywise one-tailed Bonferroni correction ($p = .017$). Then, defining acquired immunodeficiency syndrome (AIDS) as having had a CD4 count <200 or an HIV-related opportunistic infection anytime in a lifetime, we tested whether any of the six regional volumes related to history of an AIDS event (yes/no) or only a history of a CD4 count <200 (yes/no) using *t* tests and found no significant differences in brain volumes between groups with relative to those without such histories.

In the combined HIV groups, older age at final MRI correlated with length of infection ($r = .388$, $p = .00001$) and older age at HIV infection ($r = .570$, $p = .00001$). Despite these relations, only older age at MRI was predictive of frontal cortical volume deficits. Also in the combined HIV groups, a higher (worse) Veterans Aging Cohort Study (VACS) score correlated with smaller parietal volumes (Supplemental Figure S5, Table 5). A higher HAND category, indicating greater impairment, also correlated with smaller parietal volumes. Lower scores on four of the six composite measures correlated with smaller regional brain volumes: executive function with the parietal cortex; learning/memory and speed of information processing with the insular, parietal, and temporal cortices; and motor skills with the temporal cortex (Table 5).

In the Alc-only group, a higher VACS index correlated with smaller frontal volumes, and a higher HAND category correlated with smaller insular volumes (Supplemental Figure S5). In addition, lower scores on three performance composite measures correlated with smaller regional volumes: verbal/language and executive function with the temporal cortex, and

Table 3. Effects of Drug Dependence History on Six Lobar Volumes

		Frontal		Temporal		Parietal		Occipital		Insula		Cingulate	
	Sample Size	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*
Total HIV Group													
No drug history vs. control subjects	53 vs. 199	−6.028	.0000[a]	−1.214	.2698	−3.089	.0060[a]	0.966	.3339	−2.887	.0078[a]	−1.946	.0776
With drug history vs. control subjects	75 vs. 199	−5.970	.0000[a]	−3.655	.0004[a]	−4.458	.0000	1.876	.0727	−1.768	.0771	−2.378	.0261[a]
With drug history vs. no drug history	75 vs. 53	−0.536	.7100	1.792	.4386	0.669	.7100	−0.577	.7100	−1.212	.6768	0.158	.8748
HIV-Only Group													
No drug history vs. control subjects	38 vs. 199	−4.552	.0000[a]	−0.472	.6367	−2.368	.0537	1.438	.1804	−2.002	.0680	−2.047	.0680
With drug history vs. control subjects	30 vs. 199	−4.608	.0000[a]	−3.875	.0004[a]	−2.644	.0164[a]	2.5178[b]	.0177	−1.663	.1156	−1.331	.1833
With drug history vs. no drug history	30 vs. 38	0.419	.8404	3.1516[b]	.0096	0.385	.8404	−0.843	.8404	−0.115	.9082	−0.398	.8404
HIV + Alc Group													
No drug history vs. control subjects	15 vs. 199	−5.114	.0000[a]	−1.578	.2292	−3.089	.0000[a]	−0.497	.6195	−1.102	.4061	−0.621	.6195
With drug history vs. control subjects	45 vs. 199	−4.873	.0000[a]	−1.877	.0726	−4.458	.0000[a]	0.604	.5458	−2.527	.0230[a]	−2.242	.0375[a]
With drug history vs. no drug history	45 vs. 15	−1.705	.2646	−0.442	.6583	0.669	.6038	−0.827	.6038	−1.761	.2646	0.753	.6038

Alc, alcohol dependent; FDR, false discovery rate; HIV, human immunodeficiency virus; HIV + Alc, human immunodeficiency virus–infected with alcohol dependence.

[a]Significant at $p \leq .05$, FDR corrected.

[b]Volume is larger in HIV-infected individuals with drug dependence than in control subjects or HIV-infected individuals without drug dependence.

Table 4. Effects of HCV Coinfection on Six Lobar Volumes

Region	71 All HIV Without HCV vs. 89 Control Subjects		54 All HIV With HCV vs. 89 Control Subjects		54 All HIV With HCV vs. 71 All HIV Without HCV		43 HIV Only Without HCV vs. 89 Control Subjects		23 HIV Only With HCV vs. 89 Control Subjects		23 HIV Only With HCV vs. 43 HIV Only Without HCV		28 HIV + Alc Without HCV vs. 89 Control Subjects		31 HIV + Alc With HCV vs. 89 Control Subjects		31 HIV + Alc With HCV vs. 28 HIV + Alc Without HCV	
	t	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*	*t*	FDR *p*
Frontal	−3.502	.0030[a]	−5.152	.0000[a]	1.638	.3045	−2.316	.0906	−5.250	.0000[a]	2.548	.1086	−3.936	.0000[a]	−3.524	.0024[a]	−3.761	.0012[a]
Temporal	−2.171	.0598	−3.144	.0051[a]	1.075	.5652	−2.168	.0906	−2.335	.0320[a]	0.561	.8003	−1.226	.2669	−2.591	.0288[a]	−2.629	.0258[a]
Parietal	−2.335	.0585	−2.517	.0177[a]	0.336	.8100	−1.079	.3367	−2.302	.0320[a]	1.297	.3890	−2.974	.0087[a]	−1.790	.0929	−1.775	.0960
Occipital	0.529	.5969	0.765	.4441	−0.241	.8100	1.522	.1920	0.931	.3521	0.249	.8031	−1.220	.2669	0.343	.7315	0.331	.7406
Insula	−1.960	.0750	−2.353	.0224[a]	0.516	.8100	−1.811	.1402	−1.944	.0623	0.430	.8003	−1.237	.2669	−1.766	.0929	−1.751	.0960
Cingulate	−0.848	.4759	−2.783	.0108[a]	1.866	.3045	−0.555	.5789	−2.742	.0183[a]	1.992	.1392	−0.886	.3759	−1.781	.0929	−1.857	.0960

Alc, alcohol dependent; FDR, false discovery rate; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV + Alc, human immunodeficiency virus–infected with alcohol dependence.

[a]Significant at $p \leq .05$, FDR corrected.

speed of information processing with the frontal and temporal cortices (Table 5).

DISCUSSION

A central theme of this longitudinal study conducted over 14 years in patients and control subjects spanning the same age range of 25 to 75 years at study entry was to test whether HIV-infected individuals were subject to premature aging, nonaccelerated differences, or accelerated regional brain volume declines in excess of aging trajectories measured in uninfected counterparts. Compared with control subjects, the HIV-infected cohort exhibited steeper declining volume trajectories, most consistently in the frontal cortex, despite ART (50). Nonaccelerated volume deficits were detected in the temporal, parietal, insular, and cingulate lobar regions of all three diagnostic groups. Sex differences were minimal, likely given that all regional brain volumes were corrected for supratentorial volume (51). Also identified were contributions to group differences in brain volumes from alcohol and drug dependence comorbidities and from HCV coinfection. Critically, significant HIV-age interactions in lobar and selective frontal and posterior parietal volumes endured in the subset of HIV-infected individuals free of substance dependence or HCV infection compared with control subjects, thereby supporting the premise that HIV infection itself confers a heightened risk of accelerated aging of the brain, notably in the frontal lobes.

Regional Volume Deficits and Accelerated Versus Premature Aging in HIV Infection

Acceleration of volume deficits beyond normal aging was detectable in the superior frontal cortex in all three diagnostic groups. Brain regions showing accelerated aging unique to the HIV-only group were the middle and medial frontal and postcentral parietal cortices. Unique to the HIV + Alc group were deficits in midposterior cingulate and pallidal volumes. These cortical and subcortical regions are commonly affected in age-related dementing disorders, including mild cognitive impairment (52,53), Alzheimer's disease (54,55), and Parkinson's disease (56). Thus, we speculate that accelerated degeneration of this constellation of brain structures in currently nondemented people living with HIV/AIDS puts them at heightened risk for developing functional impairments that may mimic dementing disorders and ultimately interfere with activities of daily living. This is not to suggest that HIV-infected (55) individuals are at risk for developing Alzheimer's disease or other dementing diseases per se, but rather that the overlap of brain structures affected could potentially underlie selective functional declines characteristic of classical dementias (57). Further, neither length of HIV infection nor older age at infection was a significant correlate of regional brain volumes or accelerated volume decline. Rather, only age itself correlated with declining brain volumes, thereby contributing to acceleration. This uncoupling of the HIV factors, age, and brain volumes was surprising, given that individuals who are older when first infected commonly seek treatment later than individuals with younger onset do (3,4). Perhaps with further follow-up such relations will emerge.

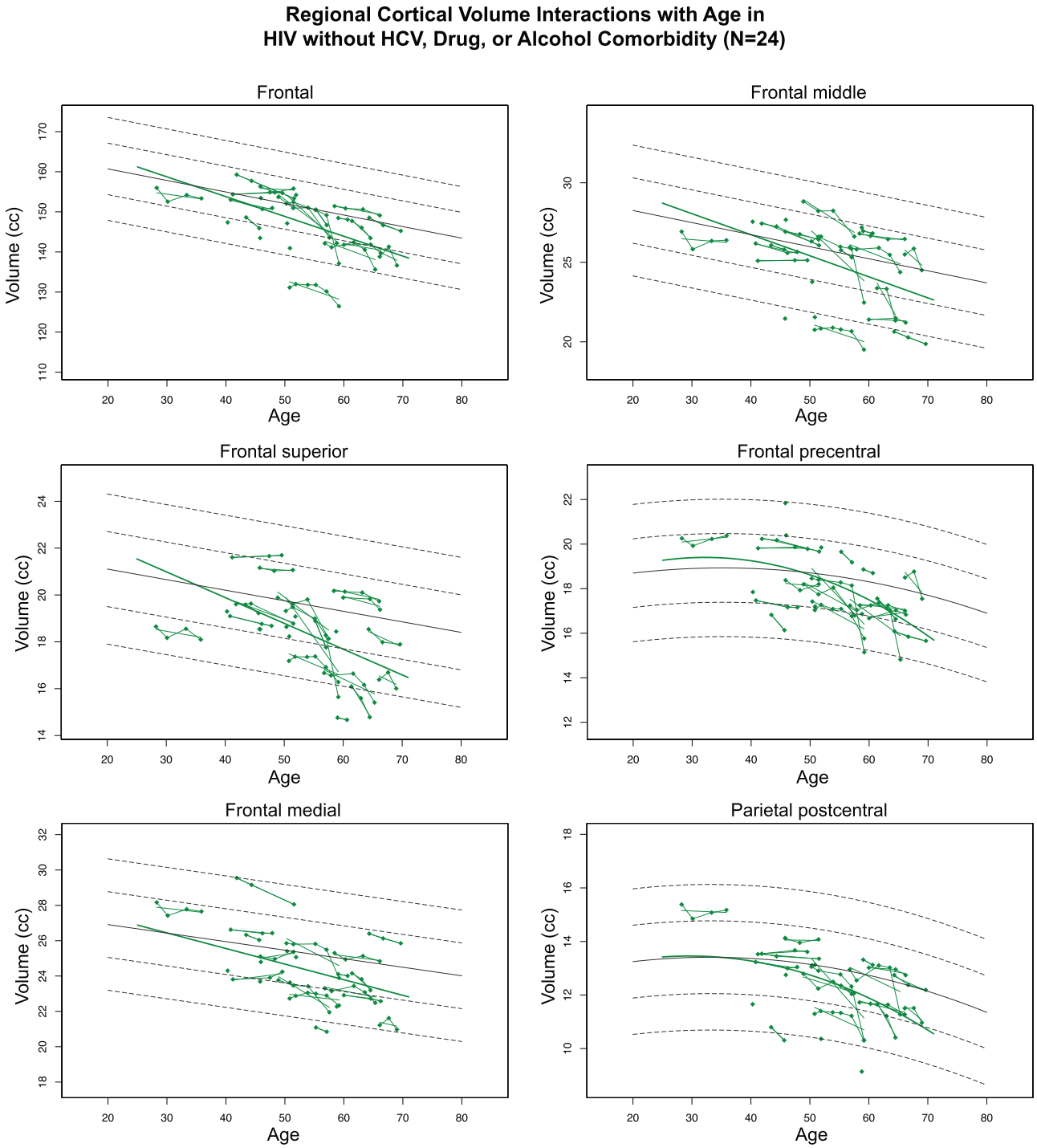


Figure 6. Scatter plots of significant age-by-diagnosis interactions in the human immunodeficiency virus–infected individuals (HIV)–only group without hepatitis C virus (HCV), alcohol, or drug dependence comorbidities indicating age-related declines in excess of those detected in the control subjects (gray regression lines).

Brain regions showing nonaccelerated volume deficits despite age correction were considered to reflect premature aging differences. We interpret these static differences as resulting from the initial infection insult without progression or improvement. Regions subject to premature aging differences were volumes of the inferior frontal and thalamus identified in

Table 5. Correlations (*r*) and *p* Values Between HIV-Related Variables and Six Lobar Volumes

	Frontal			Temporal			Parietal			Occipital			Insula			Cingulate		
	r	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*	*r*	*p*	*n*
Total HIV (HIV and HIV + Alc) Group																		
CD4 nadir before study entry	.167	.1551	74	.081	.4910	74	−.236	.0426	74	−.051	.6631	74	.039	.7424	74	.108	.3616	74
VACS	−.090	.3570	106	−.079	.4197	106	−.233[a]	.0160[a]	106	−.065	.5058	106	−.038	.6955	106	−.141	.1494	106
Length of HIV infection	.069	.4440	126	−.071	.4275	126	−.049	.5827	126	−.079	.3818	126	−.016	.8570	126	.029	.7444	126
Age at HIV infection	−.115	.2001	126	.068	.4492	126	−.034	.7034	126	.156	.0814	126	−.1752	.0497	126	−.160	.0742	126
HAND category	.035	.6991	124	−.184	.0412	124	−.330[a]	.0002[a]	124	−.040	.6562	124	−.199	.0271	124	−.066	.4658	124
Verbal/language	.088	.3403	120	.211	.0206	120	.091	.3210	120	.000	.9989	120	.124	.1778	120	.027	.7733	120
Executive function	−.002	.9861	121	.183	.0443	121	.274[a]	.0024[a]	121	.085	.3545	121	.090	.3252	121	.005	.9551	121
Learning/memory	.025	.7885	117	.424[a]	.0000[a]	117	.275[a]	.0027[a]	117	.107	.2491	117	.283[a]	.0020[a]	117	.082	.3777	117
Speed of information processing	.081	.3757	121	.296[a]	.0010[a]	121	.359[a]	.0001[a]	121	.022	.8118	121	.228[a]	.0120[a]	121	.084	.3602	121
Motor skills	.041	.6565	120	.333[a]	.0002[a]	120	.049	.5961	120	.047	.6122	120	.215	.0184	120	.077	.4025	120
Quality of social functioning	.131	.1493	123	.104	.2534	123	.103	.2571	123	.007	.9393	123	.137	.1316	123	.131	.1473	123
Days since last drink (HIV + Alc group only)	.218[a]	.0152[a]	123	.007	.9414	123	.025	.7875	123	.070	.4420	123	.012	.8927	123	.211	.0190	123
Alcoholic Group																		
HAND category	−.151	.0273	213	−.096	.1607	213	−.022	.7444	213	.084	.2229	213	−.179[a]	.0087[a]	213	−.069	.3195	213
Verbal/language	.144	.1391	107	.265[a]	.0057[a]	107	−.120	.2195	107	−.193	.0464	107	.206	.0337	107	.120	.2198	107
Executive function	.134	.1136	141	.211[a]	.0119[a]	141	−.100	.2391	141	−.131	.1228	141	.119	.1614	141	.041	.6317	141
Learning/memory	.189	.0474	111	.120	.2108	111	−.044	.6434	111	−.051	.5967	111	.134	.1608	111	.017	.8578	111
Speed of information processing	.286[a]	.0012[a]	126	.273[a]	.0020[a]	126	−.057	.5247	126	−.020	.8244	126	.209	.0186	126	.084	.3472	126
Motor skills	.174	.0641	114	−.030	.7525	114	−.008	.9286	114	−.042	.6541	114	.099	.2941	114	−.045	.6371	114
Quality of social functioning	−.011	.8726	213	−.032	.6436	213	.020	.7691	213	−.066	.3347	213	.004	.9595	213	.037	.5896	213
VACS	−.309[a]	.0002[a]	145	.168	.0440	145	.029	.7269	145	.044	.6000	145	−.018	.8317	145	−.107	.2017	145
Age at alcoholism onset	−.161[a]	.0163[a]	222	−.007	.9195	222	−.055	.4108	222	−.014	.8356	222	−.036	.5903	222	−.047	.4898	222
Lifetime alcohol consumption	−.124	.0646	222	.056	.4090	222	.052	.4415	222	.025	.7120	222	−.181[a]	.0068[a]	222	−.125	.0624	222
Days since last drink	−.015	.7651	409	−.055	.2662	409	.152[a]	.0021[a]	409	−.068	.1697	409	.094	.0570	409	.139[a]	.0048[a]	409
Alcohol consumed in the past year	−.053	.2878	409	.054	.2788	409	−.161[a]	.0011[a]	409	.168	.0006	409	.042	.3927	409	−.032	.5180	409

The six lobar volumes are means across magnetic resonance imaging scans adjusted for supratentorial volume and sex.

Alc, alcohol dependent; HAND, human immunodeficiency virus–associated neurocognitive disorder; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HIV + Alc, human immunodeficiency virus–infected with alcohol dependence; VACS, Veterans Aging Cohort Study.

[a]Exploratory correlations in the expected direction (higher composite scores and lower total HAND scores correlate with larger brain volumes) and familywise Bonferroni correction for six regions, one-tailed $p \leq .017$.

all three diagnostic groups (HIV only, HIV + Alc, and Alc only). Specific to the two alcoholic groups (Alc and HIV + Alc only) were nonaccelerated volume deficits in the middle and medial frontal and postcentral, superior, and parietal cortices; precuneus; and hippocampus. These regional deficits are largely consistent with published findings (43,58) and may represent structures that are especially vulnerable to insult from HIV infection with or without exacerbation from comorbid experience with alcohol or drugs or from coinfection from HCV.

Influence of Alcohol and Drug Dependence on Brain Volume Differences and Trajectories

Alcohol and drug abuse and dependence are frequent concomitants of HIV infection (59–61). Rather than excluding users, we directly tested the effects on brain structural volumes of these common HIV comorbidities. The alcohol and drug dependence subgroups had volume deficits in the temporal, parietal, insular, and cingulate cortices compared with control subjects, but not in excess of the drug- and alcohol-free HIV subgroups. Nonetheless, the frontal volume deficit persisted in the alcohol- and drug-free HIV-infected subgroup. Further, the two Alc groups (HIV + Alc and Alc only) had volume deficits in the superior parietal cortex, precuneus, and hippocampus, which were beyond those observed in HIV infection alone and in regions commonly affected in Alzheimer's disease (52). The question remains, however, whether these focal volume deficits present a selective liability for functional compromise to the HIV + Alc group, especially the midposterior cingulum and pallidum, which showed accelerated volumetric decline.

Contribution of HCV Coinfection to Brain Volume Differences and Trajectories

HCV coinfection is prevalent in the HIV community (62). The combined HIV groups (HIV only and HIV + Alc) coinfected with

HCV had smaller volumes of the insular, cingulate, parietal, and temporal cortices relative to their HCV-seronegative counterparts and control subjects. Thus, HCV coinfection extended the number of brain regions affected in HIV infection.

Relevance of HIV-Related Variables to Brain Volume Deficits

The VACS index predicts all-cause mortality, cause-specific mortality, and other outcomes in those living with HIV infection (63). This physiological indicator of fragility was found elsewhere to correlate with peripherally circulating levels of cytokines (monocyte chemoattractant protein 1, interferon gamma–induced protein 10, tumor necrosis factor alpha) in HIV + HCV coinfection (64). Herein, a high VACS score in the combined HIV groups correlated with smaller parietal volumes, which may be the first report of a specific brain correlate of the VACS index. Also novel is the correlation between VACS scores and frontal volumes in the Alc-only group, which could reflect declining hepatic function.

Exploratory correlations revealed that higher HAND scores, reflecting greater functional impairment, were associated with smaller parietal volumes in the total HIV group. This relation between higher HAND and VACS scores and smaller parietal volumes suggests a physiological substrate, potentially involving hepatic dysfunction, of this functional decline. We speculate that reduction or abstinence from alcohol and drug misuse and HCV treatment may have the potential to enhance physiological functioning, thereby improving affected cortical and cognitive systems. Thus, unlike classical dementias, HIV-related dysfunction, detectable in the six domains examined as part of the HAND assessment, may be reversible.

Limitations

Despite its extensive longitudinal data, this study has limitations. As a clinical investigation, we did not have access to study participants before infection onset, thereby limiting conclusions about HIV infection as the cause of identified brain volume deficits. Further, although the observations included 1101 MRI sessions and spanned upwards of 8 years per participant, the session intervals may have been too irregular to capture the dynamic progression of the infection with variation in and response to treatment. Finally, a study goal was to examine the effect of substance-dependence comorbidity and HCV coinfection on regional brain volume differences and trajectories in HIV infection rather than simply controlling or excluding for them. Although this goal was achieved, the sample sizes of resulting drug-type subsamples precluded questioning effects of specific illicit drug dependence on regional brain volumes.

Conclusions

The accelerated versus premature aging decline distinction required controlled longitudinal examination. The substantial proportion of the HIV-infected sample with a relatively late infection onset is at particular risk for either accelerated aging or premature aging brain volume deficits with compounded risk for frontal cortical involvement with alcohol-dependence comorbidity. We speculate that treatment with antiretroviral medication may have mitigated acceleration of certain brain volume deficits; alternatively, incomplete treatment or viral suppression together with coinfection or alcohol or drug comorbidities may have contributed to brain volume deficits. Indirect support of this speculation derives from the correlation between higher VACS indices and smaller parietal volumes that may potentially reflect neuroinflammatory processes notable in HIV + HCV coinfection (64) or declining hepatic functioning in alcohol-dependent individuals. In summary, the constellations of regional brain volume deficits detected in men and women living with HIV infection were associated with markers of brain injury identified with either premature or accelerated aging. Also identified were contributing comorbidities to regional brain volume decline that may be arrested with treatment of the comorbid conditions. Similarly, functional ramifications for physiological fragility and cognitive and motor decline may be mitigated or reversed with tailored ART, enhancement of healthy living practices, and reduction in consumption of harmful amounts of alcohol and drugs.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was supported by U.S. National Institute on Alcohol Abuse and Alcoholism Grant Nos. U0-AA017347, U01-AA013521, R01-AA005965, R37-AA010723, and K05-AA017168; and the Moldow Women's Hope and Healing Fund.

We thank Ehsan Adeli, Ph.D., for creating the brain images and color scales on Figures 3 and 5 and Supplemental Figures S1 and S2.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION

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Received Apr 16, 2018; revised Jun 16, 2018; accepted Jun 18, 2018.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2018.06.006.

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