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Visceral Fat is Associated with Brain Structure Independent of Human Immunodeficiency Virus Infection Status

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Abstract

The combined effects of Human Immunodeficiency Virus (HIV), obesity and elevated visceral adipose tissue (VAT) on brain structure are unknown. In a cross-sectional analysis of Multicenter AIDS Cohort Study (MACS) participants, we determined associations between HIV serostatus, adiposity and brain structure. Men (133 HIV+, 84 HIV-) in the MACS Cardiovascular 2 and magnetic resonance imaging (MRI) sub-studies with CT-quantified VAT and whole brain MRI measured within one year were assessed. Voxel-based morphometry analyzed brain volumes. Men were stratified by elevated (eVAT; ≥100cm^2) or "normal" (nVAT; <100cm^2) VAT. Forward step-

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Conflicts of Interest
JEL has served as a consultant to Gilead Sciences and GlaxoSmithKline.
MP has no conflicts of interest to report.
WSP has no conflicts of interest to report.
FJP has no conflicts of interest to report.
NS has no conflicts of interest to report.
ENM is the author of the reaction time software used in this study (CalCAP) and has a financial interest in the software.
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wise modeling determined associations between clinical and demographic variables and regional brain volumes. eVAT was present in 67% of men. Groups were similar in age and education, but eVAT men were more likely to be HIV+ and have hypertension, diabetes mellitus, body mass index >25kg/m^2, smaller gray and white matter volumes and larger cerebrospinal fluid volume than nVAT men. In multivariate analysis, hypertension, higher adiponectin, higher interleukin-6, age, diabetes mellitus, higher body mass index and eVAT were associated with brain atrophy ($p<0.05$, ordered by increasing strength of association), but HIV serostatus and related factors were not. No interactions were observed. Greater VAT was associated with smaller bilateral posterior hippocampus and left mesial temporal lobe and temporal stem white matter volume. Traditional risk factors are more strongly associated with brain atrophy than HIV serostatus, with VAT having the strongest association. However, HIV+ MACS men had disproportionately greater VAT, suggesting the risk for central nervous system effects may be amplified in this population.

Keywords

HIV; visceral fat; brain volume; brain atrophy

Introduction

Cognitive decline and structural brain changes have been described among HIV-infected persons on and off antiretroviral therapy (ART). In the absence of ART, dementia onset is associated with progression to AIDS. With suppressive ART, more subtle forms of neurocognitive decline are more common than frank dementia,(Heaton *et al*, 2010; Sacktor *et al*, 2002) and cognitive decline likely results from a combination of traditional (age, diabetes, vascular disease, obesity), HIV- and ART-specific risk factors.(Ances *et al*, 2012; Cysique and Brew, 2009) With improved control of HIV, white matter abnormalities (which are associated with cognitive impairment) have also declined in this population.(Navia *et al*, 1986; Petito *et al*, 1986)

Magnetic resonance imaging (MRI)-derived volumetric analysis is a robust method for assessing brain integrity.(Paul *et al*, 2008) While structural changes occur prior to measurable cognitive decline,(Clark *et al*, 2012) we and others have demonstrated that brain atrophy correlates with poorer neurocognitive performance in HIV-infected persons.(Becker *et al*, 2012; Cohen *et al*, 2010) In the general population, visceral adiposity and obesity have been associated with declines in cognitive function and brain volume.(Debette *et al*, 2010; Ho *et al*, 2010; Kanaya *et al*, 2009) In persons with well-controlled HIV infection, visceral adiposity and generalized obesity are common problems;(Jacobson *et al*, 2005; Sculier *et al*, 2014; Sharma *et al*, 2014) however, the contribution of metabolic disease, including obesity and lipodystrophy, to structural brain changes in HIV-infected persons is not well defined.

We designed a cross-sectional analysis of HIV-infected and HIV-uninfected men enrolled in the Multicenter AIDS Cohort Study (MACS) who underwent both MRI structural brain imaging and computed tomography (CT)-quantified abdominal adipose tissue measurement within a twelve-month period. We predicted that there would be independent effects of HIV

serostatus, ART and abdominal fat deposition on brain structure in this convenience sample of men living with or at risk for HIV infection.

Methods

Study Population

The MACS began in 1984 to study the natural history of HIV infection among men who have sex with men and to establish a repository of biologic specimens for future study. (Kaslow *et al*, 1987) Participants were enrolled from four sites (Pittsburgh, PA; Baltimore, MD/Washington, DC; Chicago, IL; Los Angeles, CA) over three time periods (1984/85, 1987/90, 2001/03), and return semi-annually for a standardized interview, clinical evaluations, laboratory tests and storage of specimens.

The MACS Cardiovascular Disease 2 (CVD2) sub-study enrolled MACS participants who were: 40-70 years of age, did not have a history of heart surgery (coronary artery bypass grafting or valve surgery) or coronary angioplasty, weighed ≤300 pounds and were able and willing to provide informed consent.(Hacioglu *et al*, 2013) Of note, men enrolled in CVD2 are generally similar to the larger MACS cohort. In 2011 and 2012, CT-quantified visceral adipose tissue (VAT) area measurements were obtained on CVD2 participants. Also in 2011, MRI brain examinations were performed on a subset of CVD2 participants, including high-resolution anatomic sequences. We conducted a nested cohort study of 226 MACS participants who 1) participated in the CVD2 and MRI sub-studies and 2) completed both CT and MRI imaging studies within a one-year period.

Clinical Assessments

Adipose Tissue Quantification—Non-contrast CT assessed VAT area in cm^2 at the L4-L5 level using a single slice. Following a centralized training, scans were performed locally (Los Angeles and Pittsburgh: 64-detector LightSpeed Volume CT scanner, GE Medical Systems, Milwaukee, Wisconsin, USA; Chicago: 64-detector SOMATOM Definition Dual Source scanner, Siemens Medical Solutions, Forchheim, Germany; Baltimore: 320-detector row AquilionONE, Toshiba Medical Systems, Tokyo, Japan) and read centrally by an experienced reader at Los Angeles Biomed (Harbor-University of California, Los Angeles, Torrance, CA), who also assessed scan quality and consistency. VAT was defined as tissue density between -190 and -35 Hounsfield units between the internal-most abdominal and oblique muscle walls and the posterior aspect of the L4-L5 vertebral body. Men were stratified by “normal” (nVAT, $<100cm^2$) or “elevated” (eVAT, $\geq 100cm^2$) VAT area, which represented both a natural break in our data and is consistent with population-base studies. (Hiuge-Shimizu *et al*, 2012; Mangili *et al*, 2015; Williams *et al*, 1996)

MRI Brain Volumetric Measurement—The MRI scanning sequences were taken from the protocol developed by the Alzheimer's Disease Neuroimaging Initiative for use with scanners with three Tesla field strengths (http://www.adniinfo.org/images/stories//mritrainingmanualv1.pdf). All scans were acquired on Siemens 3T Trio scanners (maximum gradient slew rate: 200mT/m/sec; maximum gradient strength 40mT/m), with the Siemens phase-array head coil (Basel, Switzerland). The sagittal magnetization prepared rapid

gradient echo (MP-RAGE) sequence used for this analysis was: Field of view: −256 mm; Slices: 160; Repetition time: 2300 ms; Echo time: 2.91 ms; Inversion time: 900 ms; Flip angle: 9 degrees; Thickness=1.2 mm. Following scan acquisition, de-identified MRI data was first transferred to the Image Data Archive at the Laboratory of Neuro Imaging at the University of Southern California (https://ida.loni.usc.edu/login.jsp), followed by storage on local, password-protected hard drives at the University of Pittsburgh with the last author of this report. A copy of all MRI data was also sent to the central data repository in Baltimore.

Biomarker Assessments—Circulating adipokine levels were measured under the direction of Dr. Russell Tracy at the University of Vermont Laboratory for Clinical Biochemistry Research (Burlington, Vermont, USA). Stored (−70° Celsius) fasting serum and plasma (obtained at the time of CT scan) were analyzed for adiponectin, leptin, high-sensitivity C-reactive protein (hs-CRP) and interleukin-6 (IL-6) levels. Total adiponectin, leptin and IL-6 were measured by enzyme-linked immunosorbent assays (R & D Systems, Minneapolis, Minnesota, USA). The lower limit of detection for adiponectin was 390 ng/mL, with an inter-assay coefficient of variation of 5.3-10.8%. For leptin, the lower limit of detection was 1300 pg/mL, with an inter-assay coefficient of variation range of 5.9-6.8%. For IL-6, the lower limit of detection was 0.5 pg/mL, with an inter-assay coefficient of variation range of 6.6-12.5%. hs-CRP was measured by nephelometry (lower limit of detection 0.2 μg/mL; interassay coefficient of variation range 3.0%-6.2%).

Other Measurements—Age, race, level of education, smoking history, medication use, diagnosis history and physical activity level (low, medium, high) were assessed by self-report unless otherwise defined. AIDS and other clinical events were confirmed via medical record review. Education was assessed continuously. Depression was defined as Center for Epidemiologic Studies Depression (CES-D) Scale Score >16. Hypertension was defined as resting BP >130/90, self-report of hypertension or use of anti-hypertensive medications. Diabetes was defined as self-report or use of anti-diabetic medications. Chronic Hepatitis C Virus (HCV) infection was defined as plasma HCV RNA positivity. Chronic Hepatitis B Virus (HBV) infection was defined as positive HBV surface antigen or diagnosis of chronic HBV infection. Height and weight were measured using standardized procedures and used to calculate the body mass index (BMI) in kg/m^2. Mid-waist and hip circumferences (cm) were measured using a standardized protocol,(Westat, 1988) and used to calculate waist-to-hip ratios. All socio-demographic and medical data were obtained using information collected at the MACS visit closest and immediately prior to the CT scan date. $CD4^+$ T lymphocyte subsets were enumerated using standardized flow cytometry,(Hultin *et al*, 2007) and $CD4^+$ T lymphocyte nadir was defined as the lowest count prior to and including the CT scan date. Peak HIV-1 RNA was defined as the highest value prior to and including the CT scan date.

Standard Protocol Approvals, Registrations and Patient Consents

All participants provided informed consent, and both the parent and sub-study protocols were approved by the Institutional Review Boards of the participating sites. Written informed consent was obtained from all participants prior to their undergoing research

procedures. All procedures were performed in compliance with the standards set forth by the Declaration of Helsinki. This study is registered at clinicaltrials.gov (NCT00046280).

Statistical Analysis

Metabolic and vascular variables were reduced to categorical classifications (present/absent) based on standard criteria or the distribution of values within the HIV-uninfected group. (Becker *et al*, 2009) MRI data were first processed through a non-parametric, non-uniform intensity normalization(Boyes *et al*, 2008; Sled *et al*, 1998) to reduce between-scan and between-site differences. We used a normal template image created with the Template-O-Matic (TOM8) toolbox using 68 randomly selected, HIV-uninfected men from the Information eXtraction from Images (IXI) Project (whose age distribution mimics the controls in this analysis) and estimated the prior probabilities of each tissue class (i.e., gray matter [GM], white matter [WM], cerebrospinal fluid [CSF]) for use in the segmentation routines.(Becker *et al*, 2011) We then used the Voxel-Based Morphometry-8 (VBM8) toolbox SPM12 (http://dbm.neuro.uni-jena.de/vbm8/vbm8_spm12_r442.zip) for affine-registration, normalization and segmentation of the data. The resulting GM maps were modulated to render the values in each of the 1×1×1 mm voxels as a volume, which were then smoothed using an 8×8×8 mm Gaussian filter to reduce the effects of registration error and render the data more amenable to parametric analysis.

Because participants were scanned at different sites (and on two different model scanners), we also entered three binary dummy variables to adjust for possible between-site differences. We also adjusted for enrollment cohort effect. For all analyses, the default threshold for reporting statistical significance was set at a false discovery rate of $p \leq 0.05$, with an extent threshold of 100 voxels.(Genovese *et al*, 2002) For the purposes of visualization, we projected the results onto the Colin27 standard brain.(Holmes *et al*, 1998) The mean whole brain image created from the HIV-uninfected participants was used to project all study findings.

Univariate associations between clinical and demographic characteristics and brain volume were then determined. After determining brain regions of interest for key variables, we extracted eigenvariates from the three largest regions associated with VAT and the two largest associated with BMI (Table 2). These individual volumes were extracted from 4 mm radius spheres centered on the peak voxel within each of the five regions of interest. We then used stepwise forward regression ($p<0.05$ for model inclusion) to regress these five values on significant predictor variables from the univariate analysis in the following order: age, race (white vs non-white), diabetes, hypertension, BMI (<30 kg/m^2 vs ≥ 30 kg/m^2), VAT (<100cm^2 vs ≥ 100cm^2), log IL-6 and adiponectin levels as continuous variables and HIV serostatus. For all analyses, significance was defined using a nominal, two-sided $\alpha=0.05$.

Results

Patient Population

Complete demographic and clinical characteristics of the 217 men (133 HIV-infected, 84 HIV-uninfected) included in this analysis are presented in Table 1 as a function of VAT area.

Overall, the men had mean age of 55 years, 15 years of education, BMI 26 kg/m^2, VAT 164 cm^2 and 26% were of non-white race. HIV-infected men were slightly younger (55 vs 57 years) but more likely to be of white race, have hypertension and diabetes, and had a greater mean VAT area (171 vs 151 cm^2) at a slightly lower mean BMI (25 vs 26 kg/m^2). Similarly, HIV-infected men were more likely to have eVAT (73% vs 61%), despite lower BMI. At the time of MRI scanning, the HIV-infected men had a mean CD4$^+$ T lymphocyte count of 593 cells/μL, and 82% had a plasma HIV-1 RNA level <50 copies/mL.

VAT Distribution and Associated Factors

Overall, 65% of men had elevated VAT area, with the mean in the eVAT and nVAT groups being 211 and 61 cm^2, respectively (Table 1). Men with eVAT were slightly older, had slightly higher BMIs, and were more likely to have diabetes and hypertension. HIV-infected men with eVAT had higher current CD4+ T lymphocyte counts than men with nVAT, and were less likely to have an AIDS diagnosis. GM ($F[1,214]=3.86$, $p=0.05$, $\xi_p^2=0.02$) and CSF ($F[1,214]=4.36$, $p=0.04$, $\xi_p^2=0.02$) volumes were all significantly different between the two groups, suggesting a whole brain consequence of having elevated VAT.

VBM Assessment

With regard to GM volume, univariate analysis demonstrated significant effects of age, VAT area and BMI, with a smaller effect observed for HIV serostatus (Table 2). Older age was associated with atrophy in the cingulate gyrus (including the precuneus and the anterior cingulate), insula, medial and superior frontal gyri and middle temporal gyrus (Table 2, Figure 1). BMI was significantly associated with volume in the right caudate nucleus and the left inferior frontal gyrus. VAT area, by contrast, was associated with volume in the superior temporal gyrus, insula and right caudate nucleus. HIV serostatus was associated with smaller total GM and caudate volume. There were no interactions between HIV serostatus and any factors associated with body habitus.

In the regions associated with VAT area in univariate analysis (superior temporal gyrus, insula and caudate nucleus), VAT area remained a significant predictor of these volumes after controlling for age, BMI, waist circumference, diabetes, hypertension, and adiponectin, leptin and log IL-6 levels (Table 3). Caudate nucleus volume was significantly associated with the presence of diabetes. In multivariate analysis, the effect of HIV serostatus on total GM volume was smaller and no longer statistically significant. Only a region of the caudate nucleus remained significantly associated with HIV infection after controlling for age, study site, BMI, and VFA. No other covariates demonstrated significant associations in these brain regions. Further, in an HIV-restricted analysis, no significant correlations between regional brain volumes and current or nadir CD4$^+$ T lymphocyte count, or current or peak plasma HIV-1 RNA were apparent (all r's < 0.17).

Older age and white race were significantly associated with same brain regions as BMI (right caudate nucleus and left inferior frontal gyrus [BA11]). Similarly, obesity, defined as BMI ≥30 kg/m^2, was associated with smaller brain volumes in these two regions. Log IL-6 level was also inversely associated with caudate nucleus volume, but no other biomarker associations demonstrated significant associations. No interactions were observed between

HIV serostatus, BMI, VAT area or log IL-6 level, nor did level of physical activity predict VAT area (data not shown).

Discussion

This analysis has two main findings: First, we observed significant associations between greater VAT area and higher BMI and brain volume regardless of HIV serostatus. Second, regional brain atrophy is independently associated with older age, white race, and, in the case of the caudate nucleus, by higher IL-6 levels. These data suggest that, among HIV-infected men on suppressive ART (as the vast majority of HIV-infected men were in this analysis), the relationship between visceral adiposity and brain volume is not additionally altered by HIV infection.

These data also highlight the importance of traditional risk factor management in the prevention of chronic, non-infectious comorbid disease in treated HIV infection. In fact, in this analysis we observed relationships between BMI and brain volume in participants with a mean age of 55 that were similar but attenuated compared to relationships we previously described in HIV-uninfected populations over the age of 65,(Ho *et al*, 2010; Ho *et al*, 2011; Raji *et al*, 2010) suggesting a cumulative adverse effect of obesity on brain volume over time. Further complicating this relationship is the observation that HIV-infected men may have greater VAT relative to BMI, particularly when clinical lipodystrophy is present,(Brown *et al*, 2009; Joy *et al*, 2008; Study of Fat and Metabolic Change in, 2006) a finding we also observed in this cohort. As such, it has been hypothesized that a higher prevalence of eVAT may contribute to both increased risk for and earlier onset of neurologic disease in HIV-infected persons on ART compared to HIV-uninfected controls.(Mateen *et al*, 2012) Similarly, because VAT may be elevated in the face of a “normal” BMI among HIV-infected men, BMI may not be a clinically sufficient surrogate for visceral adiposity burden in this population.

There is a potential link between visceral adiposity, chronic inflammation and brain atrophy: HIV infection is characterized by immune activation and systemic inflammation that persists in the face of suppressive ART,(Baker *et al*, 2011) and chronic systemic inflammation has been associated with neuro-inflammation, brain atrophy and cognitive decline, particularly in the hippocampus.(Daulatzai, 2014) In fact, poorer neurocognitive function has been significantly linked to abdominal obesity (as measured by waist circumference), systemic inflammation (high IL-6 levels), and immune activation in plasma (high soluble CD14 levels) and CSF (high soluble CD40L levels) in HIV-infected persons with plasma HIV-1 RNA <1000 copies/mL.(Sattler *et al*, 2014) Additionally, in older adults, higher IL-6 levels have been associated with poorer executive function.(Mooijaart *et al*, 2013; Schram *et al*, 2007) In this analysis, higher log-IL-6 levels were associated with greater caudate nucleus atrophy, supporting a relationship between chronic systemic inflammation and brain atrophy.

Another possible mediating link between visceral adiposity and brain atrophy is adipocytokine imbalance. In HIV-infected persons, visceral adiposity is associated with decreased growth hormone and adiponectin levels.(Diaz-Delfin *et al*, 2013) Leptin levels are suppressed in HIV-associated lipodystrophy but elevated in generalized obesity,(Paruthi *et*

al, 2013; Sinha *et al*, 2012) and both growth hormone and leptin replacement therapy decrease VAT in HIV-infected persons.(Diaz-Delfin *et al*, 2013; Mulligan *et al*, 2009) Adiponectin is preferentially produced by VAT, whereas leptin is preferentially produced by subcutaneous adipose tissue. Adiponectin and leptin receptors are both present in the brain, (Gustafson, 2010) and adipokine homeostasis could be important for maintaining cognitive function. Supporting this hypothesis are the findings that lower adiponectin and leptin levels are associated with cognitive impairment and brain atrophy.(Kamogawa *et al*, 2010; Lieb *et al*, 2009; Narita *et al*, 2009) Additionally, adiponectin may variably serve pro- and anti-inflammatory roles.(Hattori *et al*, 2008; Tomizawa *et al*, 2008) In this analysis, adiponectin and leptin were not significantly associated with regional brain volume, although any effect might have been overshadowed by VAT area.

This study has several limitations. First, it represents a cross-sectional analysis, and therefore cannot account for longitudinal changes in risk factors overtime. However, the MACS is a well-described cohort of HIV-infected and HIV-uninfected men, and both the HIV-uninfected control group and the sample size are strengths of this analysis. Another limitation is that our findings may not be generalizable to women or ART-naïve HIV-infected persons; however, our findings support those observed in the general population, which enhances generalizability.

In conclusion, increased VAT area, obesity and higher log-IL-6 levels were associated with regional brain atrophy in HIV-infected and HIV-uninfected men in the MACS. These findings are consistent with previously published studies in the general population, but have not previously been reported among HIV-infected persons. Additionally, HIV- and ART-specific risk factors did not predict brain atrophy. However, since HIV infection is a chronic inflammatory state and ART-treated, HIV-infected persons may have higher VAT-to-BMI ratios than HIV-uninfected persons, these findings may be important for clinical risk factor management and prevention of cognitive decline in HIV-infected adults on suppressive ART.

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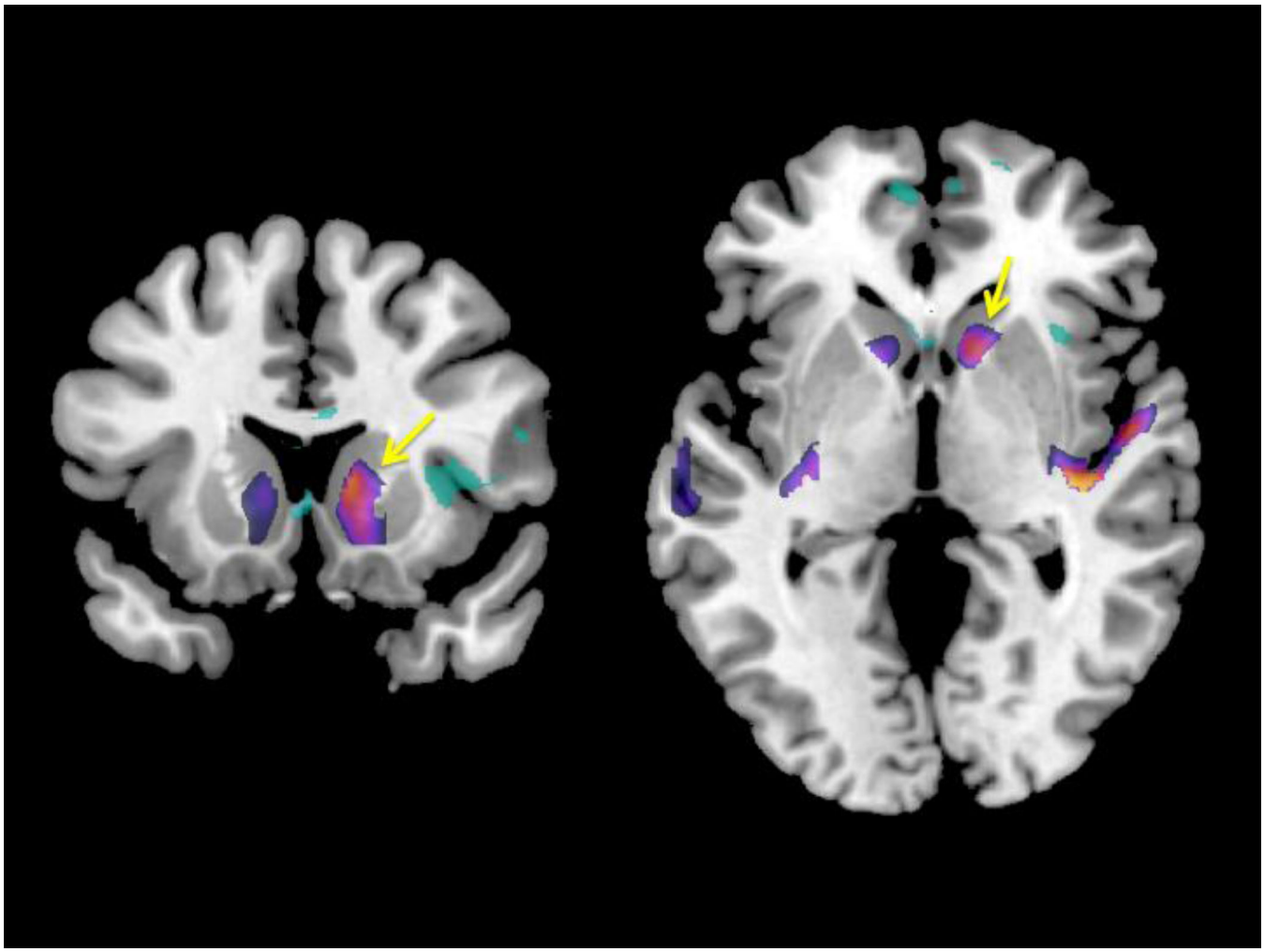

Figure 1.

Brain regions whose volumes are significantly associated with Body Mass Index (light blue) and Visceral Adipose Tissue area (purple). Areas of significant overlap in caudate nucleus are marked with arrows. The left hand image is taken in the coronal plane, and the right hand image is in the axial plane.

Table 1

Characteristics of Participants by HIV Serostatus and Abdominal Fat Volume.

	HIV-uninfected			HIV-infected			All Participants		Effect Size[1]			
VAT	**Normal**	**Elevated[2]**	**All**	**Normal**	**Elevated**	**All**	**Normal**	**Elevated**	**HIV**	**VAT**	**VAT HIV-uninfected**	**VAT HIV-infected**
Measure[3]												
Participant number	33	52	85	38	102	140	71	154				
Age (years)	56.6 (5.7)	57.7 (5.4)	57.3 (5.5)	54.1 (3.4)	55.8 (4.5)	55.3 (4.3)	55.2 (4.7)	56.4 (4.9)	−0.20 *	0.12	0.10	0.18 *
Education (years)	16.3 (2.2)	16.6 (2.6)	16.5 (2.4)	14.8 (2.8)	17.8 (11.8)	17.0 (10.2)	15.5 (2.6)	17.4 (9.7)	0.03	0.11	0.07	0.13
CESD score	11.8 (14.0)	10.2 (12.0)	10.8 (13.0)	8.7 (7.5)	9.9 (11.0)	9.6 (10.0)	10.2 (11.0)	10.0 (11.0)	−0.06	−0.01	−0.06	0.05
White Race	70 (23)	90 (47)	83 (71)	42 (16)	78 (79)	70 (95)	55 (39)	82 (126)	2.2 (1.2-4.3)	0.27 (0.15-0.50)	0.25 (0.08-0.80)	0.21 (0.01-0.47)
Enrollment Cohort 1	70 (23)	79 (41)	76 (65)	47 (18)	72 (73)	65 (91)	58 (41)	74 (114)	1.70 (0.90-3.00)	0.48 (0.27-0.87)	0.62 (0.23-1.70)	0.36 (0.17-0.77)
VAT (cm^2)	62.3 (22)	207.0 (82)	151.0 (97)	59.5 (24)	212.0 (90)	171.0 (103)	60.8 (23)	211.0 (87)	0.10	0.69 *	0.73 *	0.66 *
BMI (kg/m^2)	23.9 (3.1)	27.9 (4.2)	26.3 (4.3)	22.5 (2.6)	26.3 (4.0)	25.3 (4.0)	23.2 (2.9)	26.9 (4.1)	−0.12	0.41 *	0.45 *	0.43 *
Hypertension	30 (10)	50 (26)	42 (36)	37 (14)	48 (49)	45 (63)	34 (24)	49 (75)	1.1 (0.7-2.0)	1.9 (1.0-3.3)	2.3 (0.9-5.8)	1.6 (0.7-3.4)
Diabetes	6 (2)	17 (9)	13 (11)	3 (1)	20 (20)	15 (21)	4 (3)	19 (29)	1.2 (0.6-2.6)	5.3 (1.5-18.0)	3.2 (0.7-16.0)	9.0 (1.2-70.0)
Adiponectin (ng/mL)	11155 (6498)	7489 (3528)	8912 (5184)	11509 (7432)	6889 (4122)	8143 (5595)	11345 (6966)	7092 (3930)	−.07	−.34 *	−.28 *	−.37 *
Interleukin-6 (pg/mL)	1.52 (1.04)	1.93 (2.81)	1.77 (2.29)	4.11 (5.99)	2.07 (1.86)	2.62 (3.59)	2.91 (4.60)	2.02 (2.22)	.13 *	−.09	.06	−.16
Cocaine Use	21 (7)	10 (5)	14 (12)	40 (15)	27 (27)	30 (42)	31 (22)	21 (32)	2.7 (1.3-5.4)	0.6 (0.3-1.1)	0.4 (0.1-1.4)	0.6 (0.3-1.2)
Stimulant Use	6 (2)	4 (2)	5 (4)	8 (3)	14 (14)	12 (17)	7 (5)	11 (16)	2.9 (0.9-8.8)	1.5 (0.5-4.4)	0.6 (0.1-4.6)	1.9 (0.5-6.9)
Current $CD4^+$ T Lymphocyte Count (cells/μL)	n/a	n/a	n/a	518 (250)	620 (259)	292 (260)	n/a	n/a	n/a	n/a	n/a	0.18 *
Nadir $CD4^+$ T Lymphocyte Count(cells/μL)	n/a	n/a	n/a	238 (135)	308 (189)	289 (178)	n/a	n/a	n/a	n/a	n/a	0.01
HIV-1 RNA <50 copies/mL	n/a	n/a	n/a	68 (26)	88 (90)	83 (116)	n/a	n/a	n/a	n/a	n/a	0.29 * (0.12-0.72)
AIDS Diagnosis	n/a	n/a	n/a	24 (9)	13 (13)	16 (22)	n/a	n/a	0.6 (0.5-0.7)	0.6 (0.3-1.6)	n/a	0.5 (0.2-1.2)

[1] Point biserial correlation or relative risk (95% Confidence Interval)

[2] ≥100cm^2

[3] Mean (standard deviation) or percent (N)

* p≤0.05; VAT=Visceral Adipose Tissue, CESD=Center for Epidemiological Studies Depression, BMI=Body Mass Index, BP=Blood Pressure

Table 2

Areas of Significant[1] Associations with Grey Matter Volume.

Effect	Region	Volume (mm^3)	X	Y	Z	Z-score
Age (years)						
	Cingulate, BA32	3389	6	12	42	5.68
	Claustrum	5200	32	14	0	5.67
	Insula, BA13	6182	−38	21	2	5.88
	BA31	704	−12	−72	26	5.60
Visceral Fat Area (cm^2)						
	Superior Temporal, BA22	1891	54	−8	6	4.75
	Insula, BA13		40	−21	4	4.71
	Caudate	674	10	15	6	4.00
Body Mass Index (kg/m^2)						
	Caudate	267	51	26	4	4.64
	Inferior Frontal, BA11	369	−24	27	−24	4.45
HIV+ Serostatus	Caudate	1461	20	10	−2	3.15

BA=Brodman area (brain region)

[1] $p<0.05$

Table 3

Predictors of Regional Brain Volumes.[1]

Region	VFA-BA22	VFA-BA13	VFA-Caudate	BMI-Caudate	BMI-BA11
Predictor					
Age (years)	−0.30[2]	−0.23[2]	−0.04	−0.19[2]	−0.20[2]
White Race	−0.11	−0.05	0.02	−0.13[2]	−0.28[2]
Hypertension	−0.11	−0.14	−0.07	0.08	−0.03
Diabetes	−0.01	0.001	−0.15[2]	−0.05	−0.03
eVAT	−0.28[2]	−0.30[2]	−0.18[2]	-	-
BMI >30kg/m^2	-	-	-	−0.33[2]	−0.20[2]
HIV+ Serostatus	.03	.10	.13	.08	.06
IL-6 (pg/mL)	-	-	-	0.16[2]	0.005
Adiponectin (ng/mL)	-	-	-	−0.04	−0.04

[1] Adjusted standardized regression coefficients

[2] p<0.05; VFA=Visceral Fat Area, BA=Brodman Area, BMI=Body Mass Index, eVAT=Elevated Visceral Adipose Tissue, IL-6=Interleukin-6