Title

Abnormal Cerebral Perfusion Profile in Older Adults with HIV-Associated Neurocognitive Disorder: Discriminative Power of Arterial Spin-Labeling.

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Abnormal Cerebral Perfusion Profile in Older Adults with HIV-Associated Neurocognitive Disorder: Discriminative Power of Arterial Spin-Labeling

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ABSTRACT

BACKGROUND AND PURPOSE: The aging HIV-infected (HIV$^+$) population has increased vascular comorbidities, including stroke, and increased cognitive deficits compared with the general population. Arterial spin-labeling is a technique to measure cerebral blood flow and is more sensitive than regional volume loss in assessing neurodegenerative diseases and cognitive aging. Previous studies have found global cerebral perfusion abnormalities in the HIV$^+$ participants. In this study, we evaluated the specific regional pattern of CBF abnormalities in older HIV$^+$ participants using quantitative whole-brain arterial spin-labeling.

MATERIALS AND METHODS: CBF data from the UCSF HIV Over 60 Cohort and the Alzheimer Disease Neuroimaging Initiative were retrospectively evaluated to identify 19 HIV$^+$ older adults, all with plasma viral suppression (including 5 with HIV-associated neurocognitive disorder); 13 healthy, age-matched controls; and 19 participants with early mild cognitive impairment. CBF values were averaged by ROI and compared among the 3 groups using generalized linear models.

RESULTS: When we accounted for age, education, sex, and vascular risk factors, the HIV$^+$ participants demonstrated alterations in regional cerebral perfusion, including hypoperfusion of bilateral temporal, parietal, and occipital brain regions compared with both clinically healthy participants and those with mild cognitive impairment. Arterial spin-labeling showed reasonable test characteristics in distinguishing those with HIV-associated neurocognitive disorder from healthy controls and participants with mild cognitive impairment.

CONCLUSIONS: This study found specific CBF patterns associated with HIV status despite viral suppression—data that should animate further investigations into the pathobiologic basis of vascular and cognitive abnormalities in HIV-associated neurocognitive disorders.

ABBREVIATIONS: ADNI = Alzheimer Disease Neuroimaging Initiative cohort; ASL = arterial spin-labeling; GLMnet = generalized linear model via penalized maximum likelihood; HAND = HIV-associated neurocognitive disorders; HC = healthy controls; HIV$^+$ = HIV-infected; MCI = mild cognitive impairment; MND = mild neurologic disorder; MND = mild neurocognitive disorder

By 2013, >25% of the HIV-infected (HIV$^+$) population in the United States was older than 55 years of age, a number projected to double by 2045.[1] In this same population, the prevalence of HIV-associated neurocognitive disorders (HAND) in the United States may be up to 50%, despite access to antiretroviral therapy.[2] Cerebrovascular risk factors are prevalent in the aging HIV$^+$ population. These individuals face increased vascular comorbidities, including stroke, as well as cognitive deficits above those of the general population.[3,4] While the pathobiologic basis of vascular and cognitive abnormalities in HAND is unclear,[5] studies implicate injury to the neurovascular endothelium because HIV itself can induce endothelial dysfunction and capillary loss.[6] Indeed, virally suppressed HIV$^+$ participants have gene-expression profiles suggesting neurovascular endothelial dysfunction.[7-9] In this context, neuroimaging studies of HIV$^+$ participants consistently demonstrated increased white matter intensities[10-12] as well as altered cerebrovascular reactivity and autoregulation.[13,14] Given that small-vessel ischemic disease is associated with reduced cerebral perfusion across time[15] and hypoperfusion acts as precursor to volume loss in other neurodegenerative diseases,[16,17] several investigators have found global cerebral perfusion abnormalities in the HIV$^+$ population.[18-21] The current study evaluated the specific regional pattern of CBF abnormalities in older HIV$^+$ virally suppressed

Sample size and demographic characteristics of the cohort

	HIV+	HC	MCI
No. of participants	19	13	19
HAND-MND diagnosis	5	–	–
Age (mean) (minimum, maximum) (yr)	66.31 ± 3.09 (61, 72)	69.28 ± 4.73 (60, 74)	65.83 ± 4.19 (59, 74)
Years of education (mean)	16.74 ± 2.26	16.38 ± 2.69	16.47 ± 2.93
Sex	18 M, 1 F	13 M, 0 F	19 M, 0 F
HIV variables			
CD4 count (mean) (cells/mm³)	651.17 ± 223.98	–	–
CD4 nadir (mean)	208.65 ± 176.35	–	–
Years since diagnosis (mean)	21.5 ± 7	–	–
Undetectable viral load (% of participants)	100%	–	–
Cerebrovascular risk factors			
Myocardial infarct (No.) (%)	1 (5.2%)	0 (0%)	0 (0.0%)
Stroke (No.) (%)	0 (0%)	1 (7.7%)	0 (0.0%)
Diabetes (No.) (%)	2 (10.5%)	0 (0.0%)	0 (0.0%)
History of smoking (No.) (%)	10 (52.6%)	8 (61.5%)	8 (42.1%)
Hypertension history (No.) (%)	9 (47.3%)	4 (30.8%)	7 (36.8%)
Hypercholesterol history (No.) (%)	11 (57.9%)	11 (84.6%)	11 (57.9%)

Note:— – indicates a variable which is inapplicable to the subject group.

participants using quantitative whole-brain arterial spin-labeling (ASL).

MATERIALS AND METHODS
Participants
This study was based on 19 available cross-sectional brain MRIs from older HIV+ individuals enrolled in a larger cohort study of cognition in HIV+ individuals older than 60 years of age (UCSF HIV Over 60 Cohort) that explored the relationship between HIV and aging.[22] Five HIV+ participants in the study (26.3%) had mild neurocognitive disorder (MND) according to the Frascati criteria,[23] a HAND subcategory. To compare ASL scans from HIV+ participants and those with mild cognitive impairment (MCI),[24] we matched participants with MCI and healthy controls (HC) to the HIV participants by age, sex, and education (Table). The matched brain scans of HC and MCI participants were obtained as a part of the Alzheimer Disease Neuroimaging Initiative cohort (ADNI-2), which included ASL (inclusion/exclusion criteria at www.adni-info.org). Participants with MCI had Mini-Mental State Examination scores of >23; objective memory loss as shown on scores on delayed recall of the Wechsler Memory Scale Logical Memory II (0.5-1.5 SDs below the normal mean); a Clinical Dementia Rating scale score of 0.5 in preserved activities of daily living; and absence of dementia. All HC had Mini-Mental State Examination scores of >24 and Clinical Dementia Rating scale scores of 0. A *t* test was used to compare the distributions of age and education between those who were HIV+ and HC and between those who were HIV+ and participants with MCI, after checking that populations were normally distributed (Shapiro-Wilk test) and had the same variance (*F* test).

Cerebrovascular risk factors such as diabetes, hypertension, and hypercholesterolemia were identified through either self-report, medication list, or medical chart review and/or clinical data captured during the research visit. A 12-hour fasting serum level was obtained within 3 months of neuroimaging. Diabetes was defined as a fasting glucose level of >125 mg/dL or a current clinical diagnosis from medical history. "Hypertension" was defined as having a systolic blood pressure of >140 mm Hg or a diastolic blood pressure of >90 mm Hg; and

"hypercholesterolemia," as having a fasting low-density lipoprotein level of >160 mg/dL, a total cholesterol level of >200 mg/dL, and/or a current clinical diagnosis from medical history. "Smoking history" was defined as total tobacco use of >100 cigarettes in a lifetime.

ASL Acquisition
ASL was performed on a 3T MR imaging machine from a single vendor (Magnetom Skyra; Siemens, Erlangen, Germany) using a pulsed ASL method (quantitative imaging of perfusion using a single subtraction [QUIPPS] II with thin-slice T1 periodic saturation) with echo-planar imaging.[25] Details of ASL data acquisition and processing are available on-line at adni.loni.usc.edu. Imaging parameters of the ASL scan used the ADNI-2 protocol: FOV = 256 mm, matrix = 64 × 64, TR = 3400 ms, TE = 12 ms, TI = 700 ms, total transit time of the spins (T2) = 1900 ms, tag thickness = 100 mm, tag-to-proximal slice gap = 25.4 mm, 24 axial slices, slice thickness = 4 mm, time lag between slices = 2.5 ms.

ASL Preprocessing
All ASL images were preprocessed using an extensively described pipeline.[16,17] The ADNI investigator (D.T.) provided methods for quantitation of ASL data. Briefly, perfusion-weighted images were computed by taking the difference between the mean-tagged and the mean-untagged ASL images. The first untagged ASL image (providing a full relaxed MR imaging signal) was used as a reference image of the water density and used to calibrate the ASL signal for computing CBF and to estimate the transformation to coregister ASL and structural MR imaging.

Geometric Distortion-Correction and Structural-to-ASL Coregistration
To accomplish registration between CBF and structural MR imaging maps, we augmented linear transformation with 9 *df* based on normalized mutual information by a nonlinear registration approach based on total variance.[26]

ASL Partial Volume Effect Correction

The analysis aimed to measure blood flow in primarily gray matter tissue. To correct for gray/white matter partial volume effects, we adjusted the scaled perfusion-weighted image intensities according to a linear model of gray and white matter contributions to the ASL signal and on the basis of probabilistic segmentation of gray and white matter densities in each MR imaging voxel. Adjustments were made assuming a constant ratio between gray and white matter perfusion, and the scaled reference image was adjusted assuming constant ratios between gray matter and water, white matter and water, and CSF and water.

Computation of CBF

The scaled distortion-corrected coregistered and partial volume–corrected perfusion-weighted images were normalized to the reference image to express the ASL signal in physical units of arterial water density as CBF (Milliliters/100 g × Minute).

Structural MR Imaging Acquisition

Structural MR imaging was also acquired within the ADNI-2 and ADNI Grand Opportunities protocols for registration purposes using a T1-weighted 3D MPRAGE sequence with the following acquisition parameters: TR = 2300 ms, TE = 2.98 ms, flip angle = 9°, FOV = 256 mm, resolution = 1.1 × 1.1 × 1.2 mm^3.

ROIs

FreeSurfer (surfer.nmr.mgh.harvard.edu) was used to generate anatomic ROI statistics for CBF and volume. Eighty-two brain regions from the left and right hemispheres were used in the analysis. Areas excluded from the analysis were the brain stem, corpus callosum, ventricles, CSF, cerebellum, choroid plexus, vessels, and optic chiasm, in both the left and right hemispheres. The left sensory cortex (postcentral gyrus) was considered a reference region where no changes were expected and was used to standardize the CBF values of the other brain regions. Moreover, CBF values were adjusted to account for volume differences among ROIs.

Statistical Analysis

Because the purpose of this study was to investigate a specific pattern in CBF impairment in HIV$^+$ participants compared with HC and those with MCI, the CBF by brain regions and possible confounder factors were used as predictors of participant diagnosis (HIV$^+$ versus HC and HIV$^+$ versus MCI) under the hypothesis that if CBF in specific brain regions can be used to predict the participant diagnosis, the CBF pattern differs between HIV$^+$ and HC (or MCI). All statistical analyses were performed in R (http://www.r-project.org/).[27] HC and participants with MCI were frequency matched to HIV$^+$ participants as to age, sex, and education (2.5 SDs); however, age and education were still used in the analysis to adjust for any residual confounding.

The analyses were divided into 2 steps: 1) to create a predictive model to differentiate those HIV$^+$ from HC (respectively MCI) based on CBF, and 2) to perform casual inference by identifying the key CBF brain regions that are different between the diagnostic groups. Because of these goals, the high dimensionality of the data (82 brain regions versus 32 participants), and the high degree of multicollinearity in the data, a generalized linear model via penalized maximum likelihood (GLMnet),[28] was used to model the data. Given that our outcome variables were dichotomous (HIV$^+$ versus HC and HIV$^+$ versus MCI), the binomial family was used (logistic elastic net regression). This model uses a penalty value (L2 penalty term in the sum of squared error loss function) to shrink coefficients of correlated predictors toward each other. An additional parameter (α) combines the L1 penalty (number of zero coefficients) and L2 penalty terms. In the current modeling strategy, 10-fold cross-validation was used to optimize these 2 hyperparameters. Additionally, all predictors were centered and scaled in the analysis. Missing data were compared between groups and brain regions to ensure that imputation was acceptable.[29]

For both analyses (HIV$^+$ versus HC and HIV$^+$ versus MCI), the data were resampled 500 times by bootstrapping to ensure stable parameter estimates from the GLMnet model. At each iteration of the bootstrap, the data were randomly split into a training and test set (60% and 40%, respectively) and a GLMnet model was fit using 10-fold cross-validation of the training set. The counts for each predictor, predictor coefficients, and accuracies of the model to predict participant classification on the left-out test set were collected at each iteration. Frequency bar charts of the accuracy, specificity, and sensitivity values were plotted.

Although elastic GLMnet regression does not generate a *P* value,[30] the mean coefficient value for each brain region and corresponding 95% confidence intervals can be calculated from the bootstrap coefficient distribution. Thus, these were used to compute the odds ratios associated with each brain region by exponentiating the mean coefficients identified in the GLMnet model. The interpretation of an OR > 1 is that an increase of CBF in the corresponding brain region resulted in an increase of the likelihood of being classified as an HIV$^+$ participant. The ORs were plotted as dot-whisker plots to inspect how each brain region contributed to the ability of the model to distinguish HIV$^+$ participants from controls. Visual explanation of the processing pipeline used to obtain the model coefficients is see in On-line Fig 1.

Effect of HAND Status on CBF

As stated in the Table, 5 participants with HAND (categorized as MND) were among the HIV$^+$ participants. To study the effect of HAND diagnosis on the results of the GLMnet regression for all HIV$^+$ participants' CBF (sensitivity analysis), a GLMnet model was computed and bootstrapped 50 times with the whole cohort and again excluding the 5 participants with HAND-MND. To study the differences between the 2 sets of models, the mean coefficients for each brain region and demographic predictor were computed for each technique (including or excluding participants with HAND-MND HIV$^+$) and the differences in mean coefficients were compared with the SD associated with the corresponding predictor.

RESULTS

Participant Characteristics

Nineteen HIV$^+$, 13 age- and education frequency–matched HC and 19 age- and education frequency–matched participants with MCI were included in these analyses (Table). For all participants,
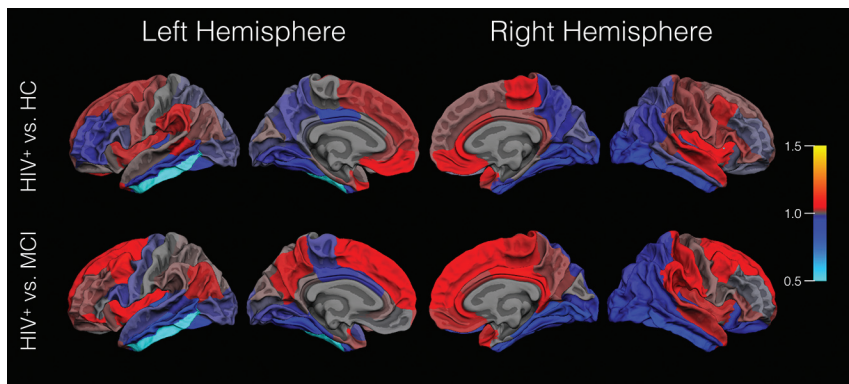
FIG 1. Odds ratio from the GLMnet model averaged over 500 bootstrap iterations. Reductions in CBF in bilateral temporal, occipital, and posterior cingulate regions best distinguish HIV+ participants from HC (blue, hypoperfusion). This same pattern of reduced CBF distinguishes HIV+ from MCI, while the latter shows comparative reductions in frontal CBF (red, hyperperfusion in HIV+ participants relative to MCI).

age ranged from 59 to 74 years old, and education ranged from 12 to 21 years. All HIV+ participants had suppressed plasma HIV RNA levels. There were 98% male participants in the whole cohort (Table). The HIV+ group included 5 participants with HAND-MND meeting the criteria for MND, and 14 cognitively healthy HIV+ participants. No participants met the criteria for HIV-associated dementia or asymptomatic neurocognitive impairment. Cardiovascular and cerebrovascular risk factors were present within the HIV+ group in proportions similar to those in the HC and MCI groups (Table).

ROI CBF Alterations

Odds ratios from the GLMnet analysis were evaluated for 82 brains regions. Figure 1 shows the whole-brain patterns of CBF changes in each diagnostic group (HIV+, HC, MCI). Cold colors reflect hypoperfusion used to accurately distinguish HIV+ participants from the second group (HC or participants with MCI). Hot colors reflect relative hyperperfusion in HIV+ participants compared with the second group. HIV+ participants are distinguished by bilateral occipital, posterior cingulate, and bilateral temporal lobe hypoperfusion relative to HC. Compared with those with MCI, HIV+ participants are distinguished by a pattern of bilateral temporal, posterior cingulate, and occipital hypoperfusion and bilateral frontoinsular hyperperfusion. The complete dataset of regional odds ratios is shown in Fig 2.

Performances of the Elastic Net Regression

The elastic net regression performed prediction of HIV+ versus HC with a median accuracy of 0.75, a median sensitivity of 0.87, and a median specificity of 0.57; and a prediction of HIV+ versus MCI with a median accuracy of 0.73, a median sensitivity of 0.75, and a median specificity of 0.71. The frequency distributions of accuracy, sensitivity, and specificity over the bootstrap are shown in Fig 3.

Effect of HAND Status on CBF

On-line Fig 2 shows the difference of mean coefficients in the GLMnet models for regional CBF when including or excluding HAND-MND from HIV+ participants (gray bars) compared with the SD associated with the corresponding predictor (black

lines) for the 2 models (HIV+ versus HC and HIV+ versus MCI). A difference in mean coefficients smaller than the associated SD was observed for all brain regions and for both models, suggesting that the presence of participants with HAND-MND was not driving CBF abnormalities in specific regions or predictors for HIV+ compared with HC or participants with MCI.

DISCUSSION

We demonstrate a significant effect of HIV+ status on regional CBF compared with age-, sex-, and education-matched controls. Based on prior work,[18-21] our primary hypothesis was that a pattern of regional cerebral hypoperfusion in HIV despite plasma viral suppression would discriminate HIV+ participants from HIV-negative participants and from those with MCI. Our data suggest a pattern of hypoperfusion in HIV that involves bilateral temporal and occipital regions previously noted to be affected by longitudinal volumetric reductions[22] in a larger sample of the same cohort (UCSF HIV Over 60 Cohort). Moreover, regional cortical thickness reductions in temporal and occipital regions were related to poor neuropsychological performance in other cohorts of treated virally suppressed HIV+ participants.[31] Most important, given volume correction as part of our data, our findings cannot be explained by structural variations in these participants; the reduction in CBF reflects perfusion within volumes rather than the effects of volume loss. These data and distribution of abnormalities are in keeping with a prior ASL analysis that was restricted to a limited set of brain slices.[18] These results suggested that an older cohort of HIV+ participants demonstrated a CBF profile that might suggest the diagnosis of HAND rather than MCI.

Few studies have evaluated quantitative CBF changes in viral-suppressed HIV+ participants. Ances et al[18] evaluated mostly untreated HIV+ participants with ASL without whole-brain coverage due to technical limitations of the available ASL technology at the time. Nonetheless, they found reduced CBF in bilateral occipital volumes and the lenticular nucleus. This prior work represents a profile of a different population, primarily of a young age and detectable viral load. More recently, Su et al[23] evaluated mean gray matter CBF using whole-brain ROIs, demonstrating reduced CBF in HIV+ participants on antiretroviral therapy. Most important, the current study includes assessment of the vascular comorbidities that often accompany HIV+ status.[32] In our study, HIV+ participants demonstrated similar rates of smoking, hypertension, and hypercholesterolemia compared with matched healthy controls and participants with MCI, though 2 HIV+ participants had a history of diabetes.

As the HIV+ population reaches geriatric age, differentiating HAND from early-stage Alzheimer disease has become a pressing HIV concern.[24] HIV-infected elders have higher rates of meeting the criteria for MCI, an intermediate state between typical cognitive aging and dementia in HIV-uninfected patient populations.[33] Comprehensive cognitive testing may discriminate the cognitive
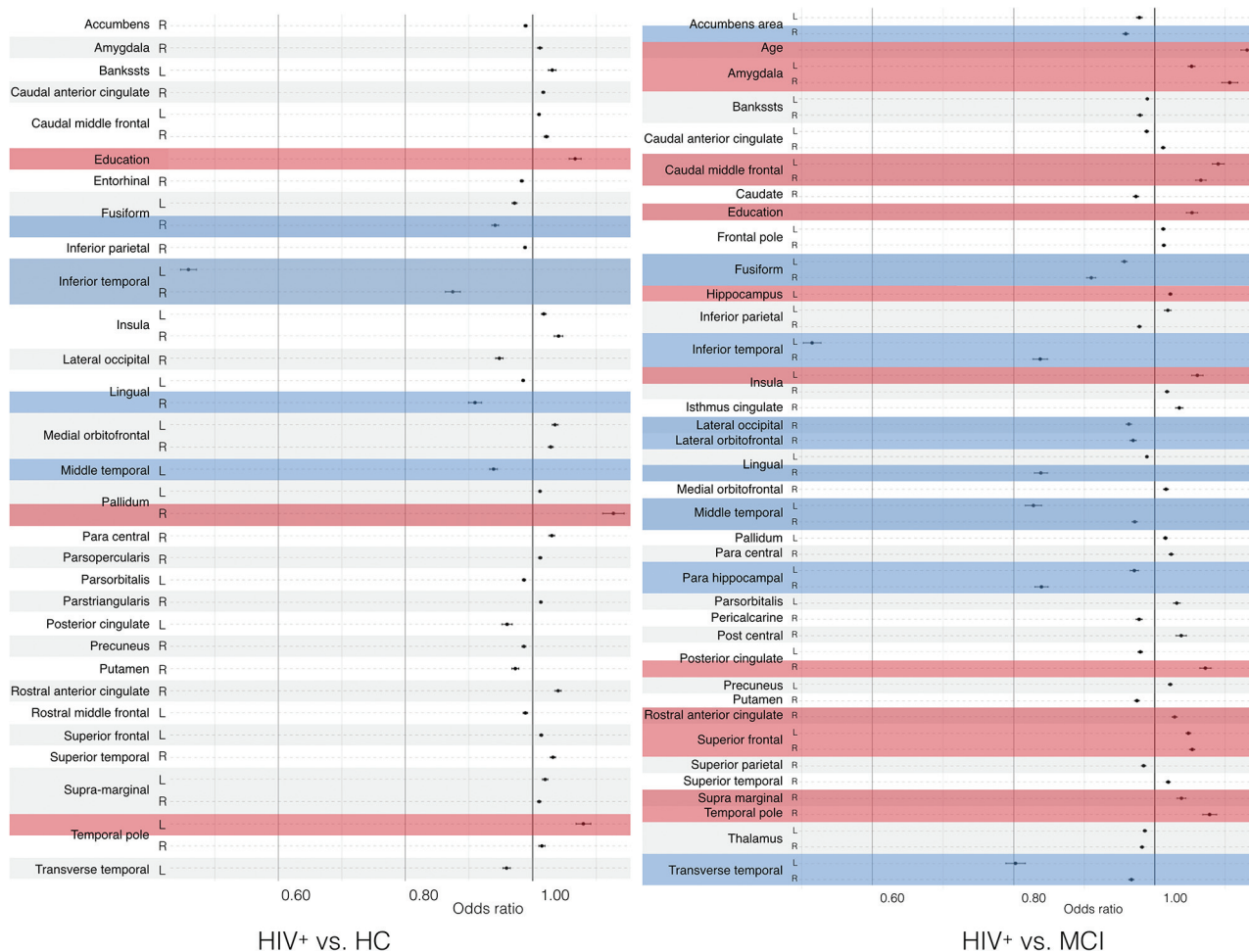
FIG 2. Odds ratios for each brain region and confounding factors in the GLMnet model, obtained by exponentiating the model coefficients averaged over a bootstrap (500 iterations). The regions used in the model in >25% bootstrap iterations are highlighted in blue for the region hypoperfused in HIV$^+$ participants and in red for regions hyperperfused in HIV$^+$ participants compared with HC or those with MCI. HIV$^+$ participants demonstrate relative hypoperfusion in bilateral temporal and occipital regions and relative frontoinsular hyperperfusion.

phenotypes of mild HAND from those of MCI due to Alzheimer disease with reasonable accuracy.[24] Here we evaluated whether CBF measurements may add specificity to the evaluation of cognitive symptoms in elderly HIV$^+$ participants. Our data suggest that CBF differences more accurately distinguish HIV$^+$ participants from HC compared with HIV$^+$ participants from those with MCI. Given temporal and parietal CBF changes within the Alzheimer disease spectrum,[17] these findings are not surprising and explain the reduced sensitivity. However, when present, the abnormal CBF pattern in HIV$^+$ participants is quite specific for the diagnosis of HIV$^+$ compared with MCI. These findings suggest that ASL CBF measurements demonstrate appropriate test characteristics for a confirmatory study after neuropsychological evaluation in elderly HIV$^+$ participants. Future work to evaluate the discriminative power of a combined cognitive and ASL CBF dataset is needed.

Sensitivity analyses were completed to examine whether CBF changes in patients with HAND-MND were driving CBF differences when comparing all HIV$^+$ participants with other groups. We evaluated whether the HAND-MND subgroup showed regional CBF differences greater than the SD of all others by comparing the mean coefficients in the GLMnet analyses. Given that

the differences between the mean coefficients of each region between HAND-MND and others were much smaller compared with the SD, the presence of HAND-MND is unlikely to explain CBF abnormalities among all HIV$^+$ participants.

The mechanisms for the observed CBF alterations within HIV$^+$ participants remain an area of active investigation. While many mechanisms might explain the interactive effects of age and HIV on the CNS, data suggest that immune activation may induce and promote cerebrovascular inflammation.[34]

Strengths of the current study include the comparison of our cohort of HIV$^+$ participants with a comparable HIV-uninfected control group and MCI group, under uniforming imaging and analysis conditions i.e. using the same ASL sequence, scanner and scanning parameters and analysis pipeline. In the existing literature, CBF measurement techniques often vary considerably among different study cohorts.[18,20,21] In addition, our analysis required no a priori hypothesis with regard to a specific region of abnormality. Another strength is the relative similarity of cerebrovascular risk factors between our HIV$^+$ participants and comparison groups, a frequent confounder of studies of CBF and vascular disease in HIV. However, these results should be interpreted cautiously along with the limitations of the study. First, because of
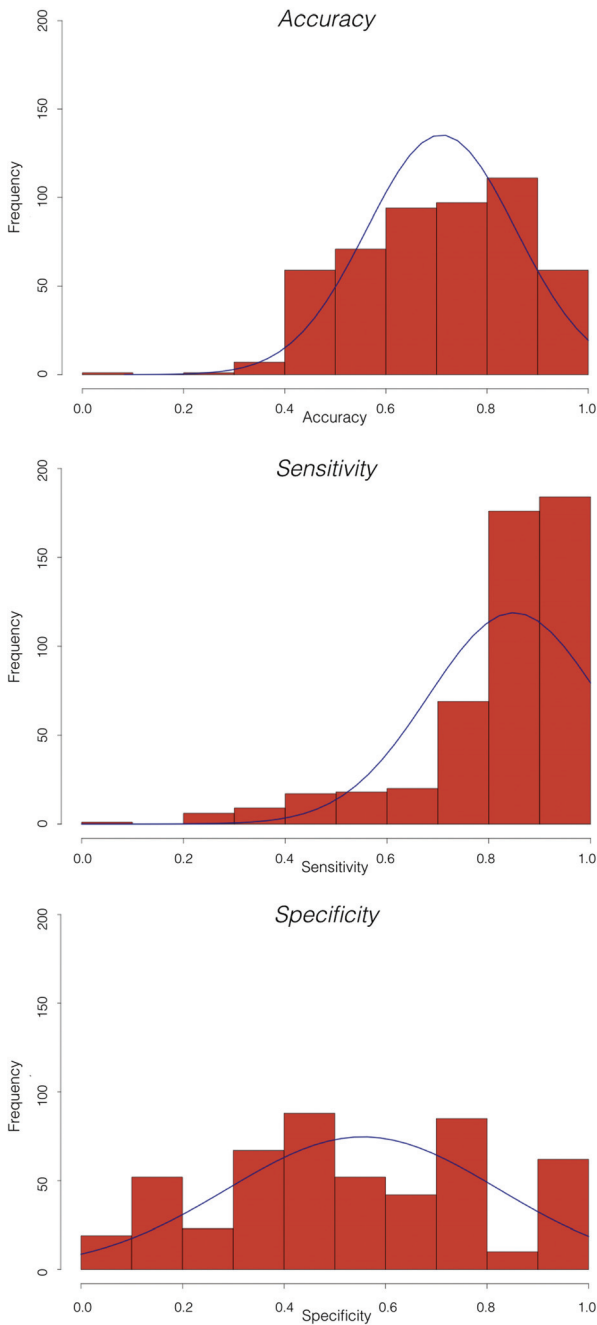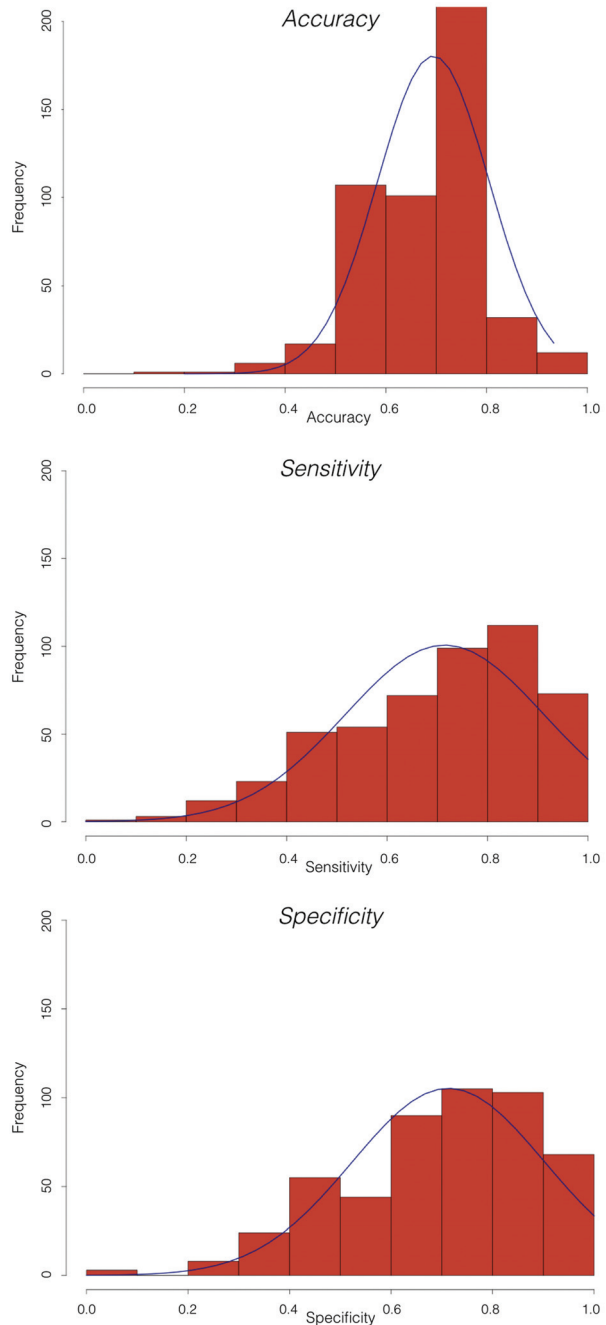
FIG 3. Histogram of the frequency distribution of accuracy, sensitivity, and specificity over the bootstrap (500 iterations) for the proposed GLMnet models.

the modest sample size, particularly in terms of uninfected controls, our findings are preliminary and need to be verified in a larger independent study. Second, this study presents an almost entirely male population, which is particularly challenging given data suggesting cerebrovascular risk in HIV may be higher in woman.[35] Finally, the age of HIV$^+$ participants reflects frequent seroconversion before the generalization of combination antiretroviral therapy, and this finding may not be generalizable to younger post-antiretroviral therapy populations.

CONCLUSIONS

When we accounted for age, education, sex, and vascular risk factors, HIV$^+$ participants demonstrated alterations in regional cerebral perfusion, including hypoperfusion of bilateral temporal, parietal, and occipital volumes compared with both clinically healthy individuals and those with MCI. Our data also add to previous reports that MR imaging–measured CBF has diagnostic ability in comparison with cognitive assessment in distinguishing HAND-MND from MCI.

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