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MAJOR ARTICLE

# The Structural and Functional Correlates of Frailty in Persons Living With Human Immunodeficiency Virus

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***Background.*** Persons with HIV (PWH) are at increased risk of frailty, a clinically recognizable state of increased vulnerability resulting from aging-associated decline in multiple physiologic systems. Frailty is often defined by the Fried criteria, which includes subjective and objective standards concerning health resiliency. However, these frailty metrics do not incorporate cognitive performance or neuroimaging measures.

***Methods.*** We compared structural (diffusion tensor imaging [DTI]) and functional (cerebral blood flow [CBF]) neuroimaging markers in PWH with frailty and cognitive performance. Virologically controlled PWH were dichotomized as either frail ($\geq$3) or nonfrail ($<$3) using the Fried criteria. Cognitive *Z*-scores, both domain (executive, psychomotor speed, language, and memory) and global, were derived from a battery of tests. We identified three regions of reduced CBF, based on a voxel-wise comparison of frail PWH compared with nonfrail PWH. These clusters (bilateral frontal and posterior cingulate) were subsequently used as seed regions of interest (ROIs) for DTI probabilistic white matter tractography.

***Results.*** White matter integrity connecting the ROIs was significantly decreased in frail compared with nonfrail PWH. No differences in cognition were observed between frail and nonfrail PWH. However, reductions in white matter integrity among these ROIs was significantly associated with worse psychomotor speed and executive function across the entire cohort.

***Conclusions.*** We conclude that frailty in PWH can lead to structural and functional brain changes, including subtle changes that are not detectable by standard neuropsychological tests. Multimodal neuroimaging in conjunction with frailty assessment could identify pathological brain changes observed in PWH.

**Keywords.** DTI; probabilistic tractography; frailty; cognition; CBF.

With the introduction of combination antiretroviral therapy, human immunodeficiency virus (HIV) is now a chronic disease with the life expectancy of persons with HIV (PWH) similar to persons without HIV (PWoH) [1]. This has led to an aging population, with more than one-half of all PWH aged $>$ 50 years old. Consequently, age-related comorbidities are becoming more common and are an increasing concern for clinicians treating PWH.

Frailty is a clinically recognizable state of increased vulnerability because of age-associated declines in multiple physiologic systems such that an individual is unable to cope with acute or consistent stressors [2]. Frail individuals, especially those older than 50 years old, are at higher risk for adverse health outcomes, such as falls, hospitalizations, and death [3]. Frailty is defined by the Fried criteria as having 3 or more of the following symptoms: unintentional weight loss, self-reported exhaustion, low physical activity, slowed gait, and/or reduced grip strength. A higher incidence of frailty has been observed in PWH compared with PWoH [4, 5]; and the presence of frailty has been linked to several clinical markers of HIV disease, including lower CD4 T-cell counts [6]. Worse neuropsychological performance, particularly in executive functioning and motor/psychomotor speed, have also been observed in frail PWH [7, 8].

There is increasing interest in identifying the biological basis of cognitive changes and frailty that are seen in PWH. A potential role exists for neuroimaging because it provides a noninvasive method to evaluate brain function and structure at the region, network, and global levels. With regard to functional neuroimaging measures, cerebral blood flow (CBF), as measured by arterial spin labeling, has been identified as a potentially valuable method to identify regions of interest (ROIs) that are affected by frailty in PWH [9]. Recent studies have observed that CBF is reduced within subcortical brain structures (ie, pallidum, amygdala, caudate, hippocampus, thalamus) of older, frail PWH [8, 10]. Notably, a machine learning model revealed that CBF was the best predictor of frailty among multiple neuroimaging modalities (CBF, brain volumetrics, and resting state functional connectivity) and cognitive performance measures [10]. However, it remains unknown if the CBF changes

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seen with frailty relate to white matter (WM) changes that are also often present in PWH [11, 12].

We use CBF and WM in a multimodality approach that allows for a greater understanding of brain structural changes in frail PWH. Measures of WM integrity were quantified with diffusion tensor imaging (DTI), a sensitive biomarker for evaluating microstructural changes in WM [13]. In a systematic review of PWoH and frailty, frailty was shown to consistently associate with worse WM integrity particularly with lower grip strength and slower gait [14–16]. Reductions in WM pathways have previously been proposed to underlie impairments in motor function and worse cognitive performance in frail PWH [17]. Prior work has shown that frail PWH have decreased WM volume, suggesting that disruption of WM pathways may be more pronounced in these individuals [18]. However, these hypotheses have not yet been tested in PWH despite increasing evidence suggesting alterations in WM microstructure are more prevalent in PWH compared with PWoH [19, 20]. The current study used a data-driven multimodal neuroimaging approach to identify affected WM tracts in older (≥50 years of age) virologically well-controlled (undetectable viral load; <200 copies/mL) frail (n = 16) compared with nonfrail (n = 100) PWH. Additionally, WM integrity, as quantified by fractional anisotropy (FA), was compared with cognitive performance (both global and domain specific).

## METHODS

### Participants

All PWH were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic, and the WUSM AIDS Clinical Trial Unit. Participants provided informed written consent that was approved by the institutional review board at WUSM. All PWH were ≥50 years old and were screened using the following exclusion criteria: current or history of confounding neurological disorders, severe depressive symptoms as assessed by the Beck Depression Inventory II (score ≥29) [21], current alcohol or substance abuse, head injury with loss of consciousness longer than 30 minutes, contraindications for magnetic resonance imaging including metal in the body or claustrophobia, seizures, or fewer than 8 years of education. All PWH had confirmed serological status, were receiving a stable combination antiretroviral therapy regimen for at least 3 months before time of assessment, and were virally suppressed (<200 copies/mL). Demographic information is provided in Table 1.

### Frailty Criteria

PWH were classified as either frail or nonfrail based on subjective and objective measures as previously defined [3]. PWH were evaluated for unintentional weight loss (>10 pounds), self-reported exhaustion, self-reported low physical activity, reduced grip strength (adjusted for sex and body mass index), and slowed gait (adjusted for sex and height). A PWH was classified as frail if he or she exhibited ≥3 of these features. For objective measures including gait and grip strength, measures were acquired in a laboratory setting under the supervision of a trained neuropsychological technician or neuropsychologist.

**Table 1. Demographic and Clinical Characteristics of Participants by Group**

| | Frail (n = 16) | Nonfrail (n = 100) | *P* |
|---|---|---|---|
| Age, y | 56.0 (7.0) | 56.9 (7.2) | .31 |
| Range | 50–74 | 50–85 | |
| Sex, N (%) | 7 (44%) M | 85 (85%) M | **<.01** |
| | 9 (56%) F | 15 (15%) F | |
| Race, N (%) | 10 (62.5%) AA | 55 (55%) AA | .91 |
| | 6 (37.5%) C | 43 (43%) C | |
| | 0 (0%) MR | 2 (2%) MR | |
| Education, y | 13.0 (2.7) | 13.5 (2.6) | .46 |
| Range | 9–18 | 8–18 | |
| Recent CD4 T-cell count; median (IQR) | 688 (414, 741) | 563 (359, 827) | .13 |
| Nadir CD4 T-cell count; median (IQR) | 180 (40, 273) | 78 (19, 247) | .20 |
| Plasma viral load (copies/mL, $\log_{10}$) | 1.3 (0.1) | 1.4 (0.2) | .49 |
| Global cognition *Z*-score | −0.5 (0.7) | −0.2 (0.6) | .08 |
| 10-y Framingham Risk Score | 17.7 (10.5) | 18.1 (9.2) | .88 |
| Range | 11–23 | 16–20 | |
| Area Deprivation Index National Rank | 76.7 (22.7) | 70.1 (24.9) | .34 |
| Range | 38–99 | 8–100 | |

Abbreviations: AA, African American; C, Caucasian; F, female; IQR, interquartile range; M, male; MR, more than 1 race. Significant differences between Frail and Nonfrail ($p < 0.05$) are designated in bold.

### Cognition

All PWH completed a comprehensive neuropsychological battery that included tests evaluating 4 cognitive domains: psychomotor speed (Trail Making Test A [22], Digit Symbol [23], Grooved Pegboard dominant and nondominant hands [24], Symbol Search [23]), learning and memory (Hopkins Verbal Learning Test free recall and both learning trials [25], Brief Visuospatial Memory Test free recall and both learning trials [26]), executive function (Color-Word Interference Test [27], verbal fluency [28], Trail Making Test B [22], Letter Number Sequencing [23]), and language (Letter Fluency [29], Category Fluency [30]). These tests have previously been used to assess cognitive impairment in PWH [31]. Raw test scores were converted to standardized scores (*Z*-scores) using published norms that adjusted for demographic variables (age, sex, race, and years of education) when applicable. Test *Z*-scores within a single cognitive domain were averaged to create domain *Z*-scores. These domain *Z*-scores were then averaged to create a global cognition *Z*-score.

### Imaging Acquisition

All imaging was performed on a 3T Siemens Tim TRIO scanner (Siemens AG, Erlangen, Germany). The imaging protocol

included structural T1-weighted, DTI, and pseudocontinuous arterial spin labeling (pCASL) sequences. High-resolution 3D magnetization-prepared rapid acquisition of gradient echo (MP-RAGE) images were collected in the sagittal plane using a 12-channel head coil. A total of 176 slices, 1.0-mm slice thickness, and voxel dimensions of $1.0 \times 1.0 \times 1.0$ mm were acquired. CBF was derived from the pCASL method using the following sequence: 1.5-second labeling time, 1.2-second post-labeling delay, repetition time of 3500 ms, echo time of 9.0 ms, $64 \times 64$ acquisition matrix, 90° flip angle, 22 axial slices with a 1-mm gap, and voxel size of $3.4 \times 3.4 \times 5.0$. Two pCASL scans were acquired, each containing 60 volumes (30 pairs) of control and label volumes and a duration of 3.5 minutes. Two sequential DTI scans were obtained ($2 \times 2 \times 2$ mm voxels, repetition time = 9900 ms, echo time = 102 ms, flip angle = 90°, 23 directions, b-values ranging from 0 to 1400 seconds/mm$^2$), and 1 nondiffusion-weighted image.

#### CBF Preprocessing

Image preprocessing was performed using the FMRIB Software Library (FSL, Oxford, UK) [32]. pCASL $M_0$ images were brain extracted and linearly aligned to T1-weighted images. All T1-weighted images, and the corresponding pCASL $M_0$ images, were registered to the Montreal Neurological Institute (MNI152) 1-mm brain before analyses. pCASL volumes were motion-corrected; frame pairs with >0.5-mm displacement between label and control were censored. CBF was calculated by pairwise subtraction of spin-tagged and untagged images using a standard single-compartment model that follows recommended clinical guidelines [33]. Voxels with nonphysiological CBF (<0 or >120 mL/100 g/min) were excluded.

#### CBF Postprocessing

A linear regression model was used to adjust CBF values for group differences with regard to age and gender. Residuals from these models were used in subsequent analyses. PWH were dichotomized based on frailty status, and group differences were analyzed on a voxel-wise basis to evaluate for regional differences in CBF. A cluster-based technique was performed across gray-matter voxels to correct for multiple statistical comparisons. Random-effects maps, thresholded at $P < .05$, were permuted to compute a distribution of cluster size occurrence. A minimum cluster size of 40 voxels was determined based on a $P = .05$ occurrence threshold with all significant voxels belonging to clusters smaller than this threshold excluded.

#### DTI Preprocessing

Preprocessing included correction for motion and eddy current distortions followed by skull stripping using FSL [34]. Scans were inspected to ensure that head movement was <3.5 mm for all participants during data acquisition. Tensors were estimated with FA maps created using DTIFIT in FSL [35]. FA was the primary metric evaluated. All images were smoothed with a 3-mm smoothing kernel to address potential partial volume effects. All FA maps were warped to MNI space via the reference FMRIB_FA_1 mm, a template in MNI space that has been optimized for diffusion images.

#### WM Tract Preprocessing

To generate WM tracts, cognitively normal healthy PWoH (aged 22–35 years; n = 144) from the Human Connectome Project were selected after rigorous screening of all data (humanconnectome.org/documentation). These individuals were only used to generate a WM connection template that was seeded from regions of differential CBF as identified previously.

Significant ROIs generated from the prior CBF analysis were used as seeds for the probabilistic tractography algorithm Probtrackx in FSL [36]. WM projections connecting the interface voxels between each ROI were created by FMRIB Software Library's (FSL's) probabilistic pipeline. This pipeline consisted of correction for EPI distortions, eddy-current induced distortions, participant motion, and gradient nonlinearities with TOPUP and EDDY from FSL [37].

Full details regarding the generation of WM tracts for patient populations using the human connectome project (HCP) data has been previously published [19]. In short, bedpostX from FSL was used to quantify diffusion orientation distributions from preprocessed HCP DTI data. This tool uses Markov chain Monte Carlo sampling to calculate the dominant and secondary fiber distributions for each voxel. Each ROI identified by CBF was subsequently warped into native space before performing tractography. For each CBF ROI pair, probabilistic tractography was performed twice, with each ROI serving as the seed or the target and the average of the results used to identify connections between the 2 ROIs. Once completed, a threshold for each probabilistic mask was identified as 10% of the maximal intensity to reduce sporadic projections. Each of the probabilistic masks were warped into the MNI space using a combination of linear and nonlinear alignments. Probabilistic masks pertaining to a particular tract were combined and then limited to voxels present by a simple majority.

#### WM Postprocessing

WM tracts connecting each ROI seed identified by CBF were analyzed independently as well as compiled into a "network" that included the average WM integrity from all WM tracts that connected all ROIs. Each WM tract was overlaid onto the FA map of each PWH to extract FA values from voxels residing within it. Additionally, FA values were also extracted from an atlas based corticospinal tract, which served as a control pathway [38]. A nonparametric Mann-Whitney of the medians was used to evaluate differences between frail and nonfrail PWH after controlling for age and sex. A statistical threshold of $P < .05$ was used for each WM tract.

#### Comparison Between DTI and Cognition Measures or HIV Variables

Domain and global cognition *Z*-scores were first compared between frail and nonfrail PWH using Mann-Whitney *U* tests. Next, the average FA from each WM tract was compared with cognitive measures. We evaluated the relationship between tract FA values and global cognitive performance across the entire cohort with linear models with age and sex treated as covariates. Similar linear regression models were also performed for each of the cognitive domains (learning and memory, language, psychomotor speed, and executive function).

Finally, the average FA from each WM tract was compared with select HIV variables measuring previous and current HIV severity (nadir and current CD4). The linear models were performed with age and sex treated as covariates.

## RESULTS

#### Demographics

The cohort consisted of PWH (n = 116) of whom 100 were nonfrail and 16 were frail. The 2 groups were not significantly different with regard to age, race, or education but did differ with regards to sex ($P < .01$). The 2 groups had similar CD4 nadir, CD4 current, and plasma viral loads. For additional details regarding demographic information, see Table 1.

#### CBF Analysis

After correcting for multiple comparisons, frail PWH had significantly lower CBF in 3 clusters compared with nonfrail PWH. Two clusters resided within the frontal cortex, and 1 was in the posterior cingulate (Figure 1). No regions were identified where nonfrail PWH had significantly lower CBF compared with frail PWH. These 3 ROIs were subsequently used as seed regions for WM tract analyses.

#### WM Tract Analysis

Average FA values for the tracts that connected each of the ROIs identified by CBF were compared for nonfrail and frail PWH. Frail PWH had a significant reduction in FA compared with nonfrail PWH for tracts that connected frontal ROIs to the posterior cingulate (left frontal $P = .0097$; right frontal $P = .0177$). Connections between the 2 frontal ROIs were also reduced but at a trend level ($P = .067$). Overall, the average FA from WM tracts that connected these 3 ROIs was significantly lower for frail compared with nonfrail PWH ($P = .026$). No differences were seen between frail PWH and nonfrail PWH for the corticospinal tract ($P = .22$), which served as a control. These results suggest a specificity in WM tracts involved.

#### Cognition and HIV Factors

No differences were observed in terms of cognition for either domain or global metrics between frail and nonfrail PWH ($P$ values $> .05$). Across all PWH, the average FA from the WM "network" was significantly correlated with global cognition ($F = 5.41$, $R^2 = 0.037$, $P = .022$). When analyzing each domain separately, WM integrity was significantly associated with psychomotor speed domain ($F = 9.62$, $R^2 = 0.067$, $P = .003$) and executive function ($F = 7.17$, $R^2 = 0.051$, $P = .009$) but not language ($F = 0.3$, $R^2 = 0.004$, $P = .79$) or memory ($F = 0.674$, $R^2 = 0.006$, $P = .41$). Figure 2 shows the relationship between the structural connectivity among the ROIs and psychomotor speed. No relationship was observed for any of the WM tracts with either current or nadir CD4 as an analysis of HIV severity.

## DISCUSSION

Frailty is categorized as a signature of a possible underlying comorbidity and is traditionally more prevalent in PWH compared with HIV-negative controls. For our cohort, we observed a prevalence of 14%, which is within an expected range for PWH [39–41]. We observed that PWH who were frail had worse brain integrity. Our findings revealed that in the absence of cognitive impairment characterized by neuropsychological assessment, imaging correlates of structural and functional integrity were reduced in frail compared with nonfrail PWH. PWH who had higher structural integrity, as assessed by FA using DTI, performed better on tests of psychomotor speed and executive function. Therefore, incorporating multimodal imaging metrics with frailty assessment may identify PWH who are potentially at greater risk for future cognitive decline.

This novel methodological approach used CBF to derive data-driven ROIs to evaluate WM pathways. Treating these regions as subsequent seed ROIs allowed us to generate more accurate representations of WM pathways in PWoH (HCP individuals). We focused on these WM pathways instead of implementing techniques like tract-based spatial statistics that are designed for studies without a specific hypothesis [42]. We assessed the localizability of our findings by including the corticospinal tract that was not identified by functional ROIs. This tract did not differ between the frail HIV and the nonfrail HIV groups, suggesting our findings were not global but specific to frailty in HIV.

We observed regional reductions in CBF in frail PWH compared with nonfrail PWH. Frontal regions, including the dorsal lateral prefrontal cortex, are often affected in PWH and could lead to impairments in decision-making [9]. The precuneus and cingulate cortices were also identified, and these results corroborate prior findings that showed an association between atrophy in this region with reduced quality of life in PWH [43]. WM integrity between these ROIs differed by frailty status. Previous work for evaluating frailty in PWoH has led to mixed results. Some studies have shown robust DTI changes throughout the brain [44], whereas others found more localized

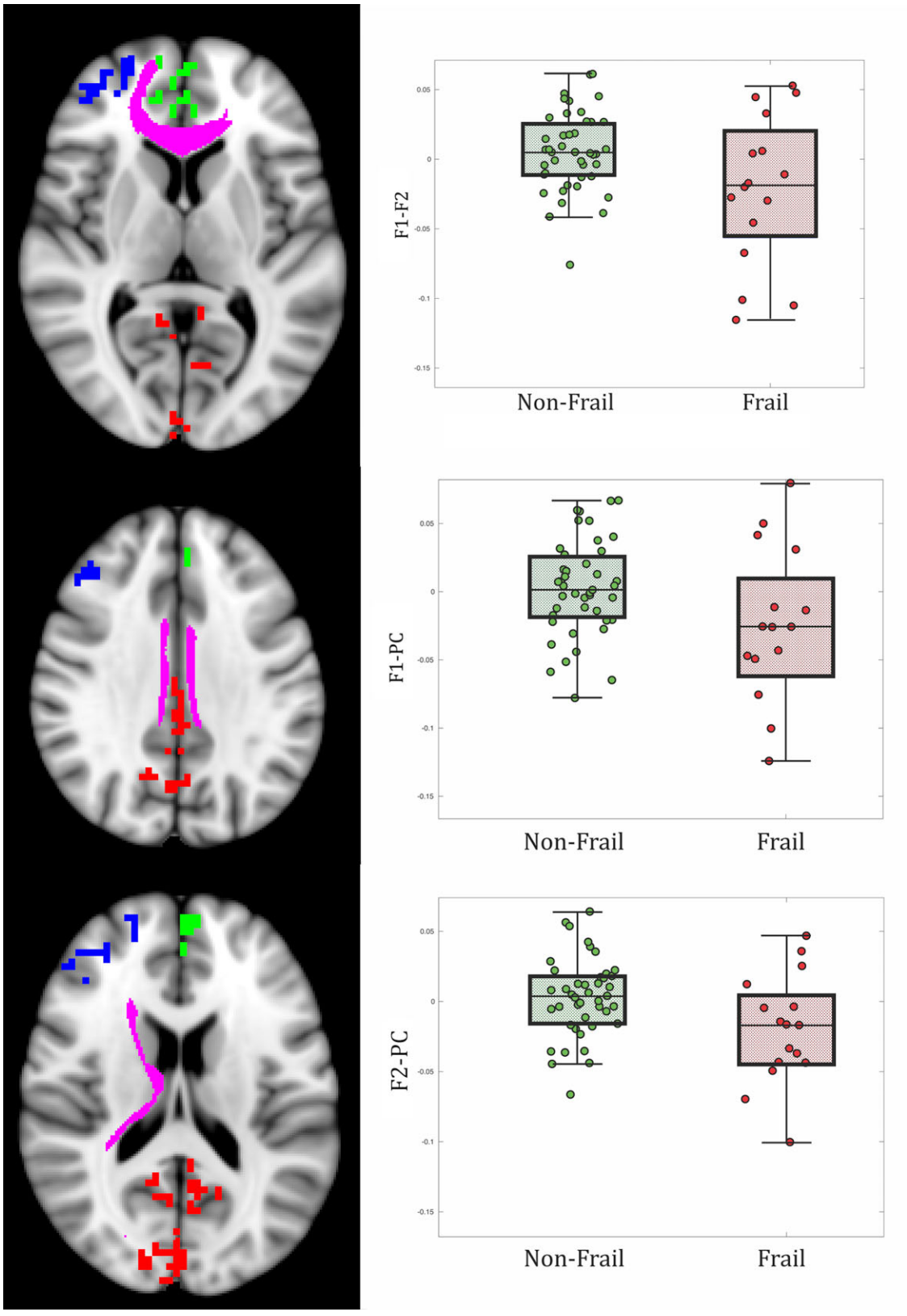


**Figure 1.** Persons with HIV (PWH) who were frail had significant decreases in cerebral blood flow (CBF) within 3 regions of interest (ROIs), including the frontal left (F1) = blue, frontal right (F2) = green, and posterior cingulate (PC) = red) compared with nonfrail PWH. The connections between the various CBF ROIs are displayed in magenta. The boxplots represent the structural integrity of the designated white matter (WM) tracts for the frail and nonfrail PWH groups. Significant differences were observed for WM connections between F1-PC and F2-PC.

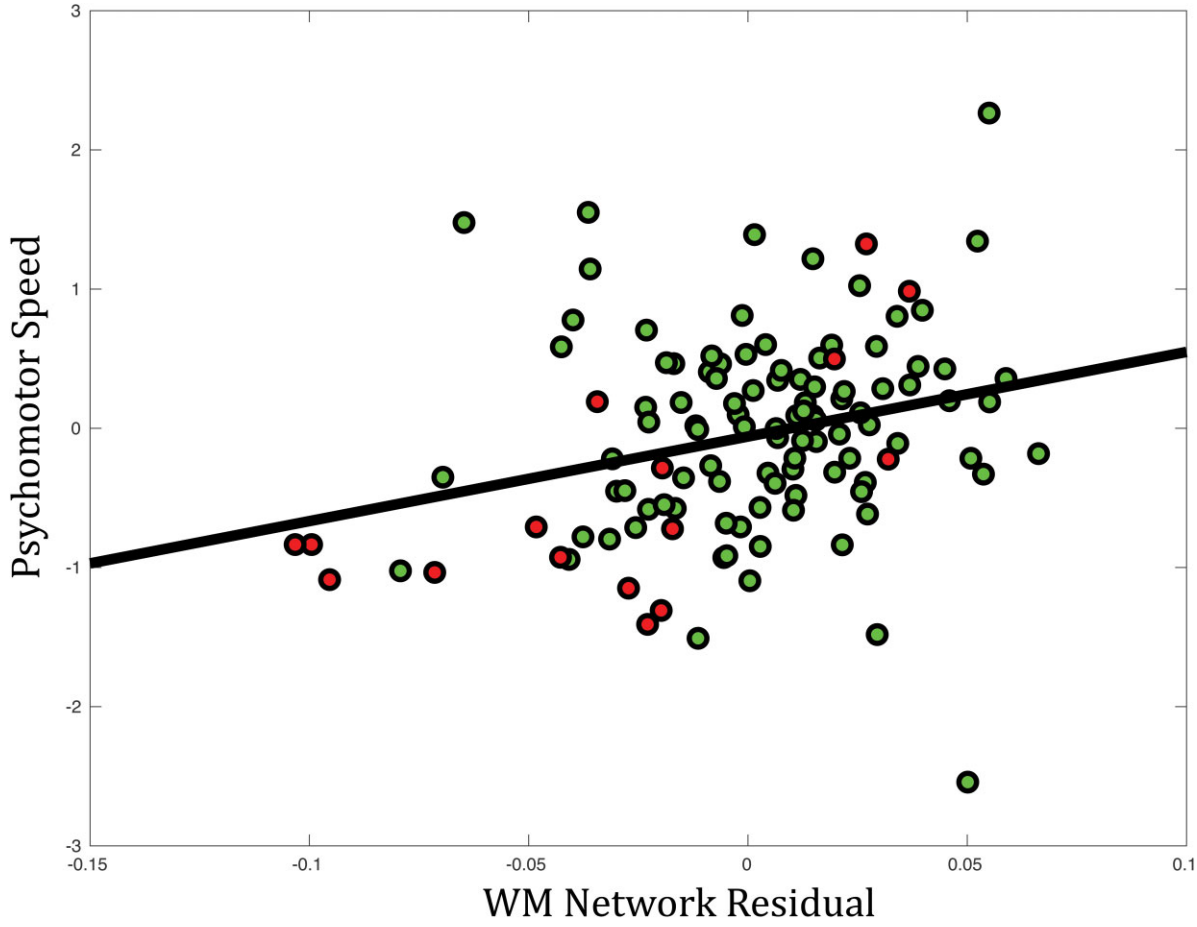


**Figure 2.** The relationship between average WM connections among the ROIs identified by CBF as a function of psychomotor speed for the entire PWH cohort. Frail PWH are indicated in red and nonfrail PWH are indicated in green. CBF, cerebral blood flow; PWH, people with HIV; ROI, region of interest; WM, white matter.

changes, with primarily callosal regions or frontal WM regions affected, similar to our findings [16, 45].

Across all participants regardless of frailty status, reductions in WM integrity were associated with worse performance in the psychomotor speed and executive function domains. Both cognitive domains are known to be affected by HIV [46]. Prior work has identified significant relationships between these domains and changes in WM microstructure in older PWoH [47]. We did not observe differences between frail and nonfrail PWH with regard to cognition. In contrast, significant differences in neuroimaging metrics of both structure and function were observed between the 2 groups. Our cognitive results are similar to previous studies that did not observe significant differences between frail and nonfrail PWH after sex was included as a covariate [8]. Our results suggest that brain imaging measures of integrity may be more sensitive than behavioral assessments for evaluating frailty in older PWH.

There are several limitations with the current analyses. Future studies with larger sample sizes are needed to improve our understanding of the findings discussed in this paper. Our cohort did not contain sufficient data on activities of daily living to determine HAND criteria. Longitudinal data are necessary to determine the trajectory of the frail individuals and to monitor their cognitive and imaging outcomes. We focused on older ($\geq$50 years) frail individuals and cannot be extrapolated across the entire age range. Finally, the Fried Frailty measurement is a generic tool for underlying comorbidity but has been extensively used in PWH as an indicator of increased risk of possible future cognitive decline and poorer disease outcomes.

Overall, these results implicate an underlying reduction in brain integrity imaging measures for frail PWH compared with nonfrail PWH. Frailty associated with reductions in brain structure and function in virologically well-controlled older PWH. Lower CBF and reduced WM integrity was observed in frail compared with nonfrail PWH despite no differences in cognitive or virological measures (ie, CD4 nadir or current). Our data demonstrated that reductions in WM integrity from frailty associated with worse performance on psychomotor speed and executive function tasks. HIV-associated variables did not associate with WM integrity, suggesting that the changes are due to frailty and not severity of HIV disease. Further longitudinal studies are needed to determine if observed

changes in brain structure and function remain stagnant or continue to progress and lead to cognitive decline in older PWH.

## Notes

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***Potential conflicts of interest.*** B. M. A. reports a patent for use of plasma NfL for CAR-T neurotoxicity (to institution and not relevant to manuscript); and an unpaid leadership or fiduciary role on the Editorial Board of Journal of Neurovirology. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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