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Abnormal Magnetic Resonance Image Signature in Virologically Stable HIV Individuals

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Background. With implementation of combination antiretroviral therapy (cART), changes to brain integrity in people with HIV (PWH) are subtle compared to those observed in the pre-cART era. T1-weighted/T2-weighted (T1w/T2w) ratio has been proposed as a measure of cortical myelin. This study examines T1w/T2w values between virologically controlled PWH and persons without HIV (PWoH).

Methods. Virologically well-controlled PWH (n = 164) and PWoH (n = 120) were compared on global and regional T1w/T2w values. T1w/T2w values were associated with HIV disease variables (nadir and current CD4 T-cell count, and CNS penetration effectiveness of cART regimen) in PWH, and as a function of age for both PWoH and PWH.

Results. PWH had reduced global and regional T1w/T2w values compared to PWoH in the posterior cingulate cortex, caudal anterior cingulate cortex, and insula. T1w/T2w values did not correlate with HIV variables except for a negative relationship with CNS penetration effectiveness. Greater cardiovascular disease risk and older age were associated with lower T1w/T2w values only for PWH.

Conclusions. T1w/T2w values obtained from commonly acquired MRI protocols differentiates virologically well-controlled PWH from PWoH. Changes in T1w/T2w ratio do not correlate with typical HIV measures. Future studies are needed to determine the biological mechanisms underlying this measure.

Keywords. myelin; HIV; T1w/T2w.

Since the introduction of combination antiretroviral therapy (cART), the life expectancy of people with HIV (PWH) has significantly improved and is approaching that of people without HIV (PWoH). Although the severity of cognitive impairment associated due to human immunodeficiency virus (HIV) has continued to diminish, milder cognitive impairment and changes in brain integrity persist in PWH on stable cART. Methods that identify these subtle brain changes in PWH are vital for evaluating the effectiveness of adjunctive therapies for PWH.

Neuroimaging represents a noninvasive method to identify changes to brain structure and function. While widespread use of cART has reduced the magnitude of macrostructural brain changes observed in PWH [1], white matter changes persist. For example, white matter hyperintensity load is higher in well-controlled PWH compared to PWoH [2]. Additionally, robust reductions in microstructural white matter integrity have been observed using diffusion tensor imaging (DTI), despite virological control with cART [3]. DTI is currently considered the most sensitive method to capture subtle changes to myelin and brain white matter integrity in PWH. However, this technique has several disadvantages, including a lack of specificity to myelin integrity, low sensitivity to cortical white matter, and it cannot account for the influence of crossing fibers on generating regional white matter values. Additionally, DTI acquisition is sometimes difficult and is not consistent. Consequently, novel techniques that utilize imaging modalities that are acquired in most standard imaging protocols to identify subtle white matter changes in PWH would be beneficial.

The T1-weighted/T2-weighted (T1w/T2w) ratio was initially proposed as a method for quantifying cortical myelin concentration [4]. This metric relies on the relative signal intensity of T1-weighted and T2-weighted images that are typically acquired. High T1w/T2w signals are seen in areas with increased cortical myelination, with change across the lifespan. This ratio is derived from the neuroimaging properties of the T1w image. The white matter and pial surface can be isolated from the T1w image by the suppression of signal from the dura and blood vessels, which is performed by dividing the T1 signal by the T2w image [5]. Prior work mapping this ratio across the human cortex has demonstrated a close resemblance to the distribution of myelin fibers seen with myeloarchitectonical studies [6]. In healthy individuals, the T1w/T2w ratio is sensitive to age-related

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changes in intracortical myelin and correlates with cognitive performance [7]. This technique has also successfully identified white matter changes in several neurodegenerative and neuroinflammatory diseases. For example, a decrease in the T1w/T2w signal has been repeatedly observed in multiple sclerosis [8–11] and schizophrenia [12]. Conversely, an increase in the T1w/T2w ratio has been observed in Parkinson disease [13], Huntington disease [14], and Alzheimer disease [15]. Overall conclusions from these studies indicate that both very low T1w/T2w ratio and very high T1w/T2w ratio, particularly in conjunction with the presence of other disease pathology, may indicate abnormal changes to the microstructural white matter and myelin content of the brain.

Despite known white matter changes in PWH, the T1w/T2w ratio has not been well studied in PWH. One recent study has examined differences in the T1w and T2w signals between PWH who were either taking or not taking cART and healthy controls [16]. However, the number of participants included was very small (n = 12). An established pattern of T1w/T2w ratio in a well-characterized sample of PWH who are virologically well controlled would allow clinicians and researchers to generate a more complete picture of brain integrity using simple scans that are already typically acquired during a magnetic resonance imaging (MRI) scan. This study evaluated both the global and regional T1w/T2w ratio in PWH and PWoH. Additionally, T1w/T2w ratios were examined with regards to HIV disease variables (CD4 T-cell count, nadir CD4 T-cell count, CD8 T-cell count, CD4/CD8 ratio, duration of infection, and cART regimen). Finally, the relationship between age and the T1w/T2w ratio was evaluated across the lifespan for PWH and PWoH.

METHODS

Study Participants

All data was acquired between 2010 and 2017 and PWH were recruited (n = 164) from the Infectious Disease Clinic and AIDS Clinical Trial Unit at Washington University in St Louis. PWoH (n = 120) were recruited from the St Louis community or research participant registry.

Study inclusion criteria included more than 8 years of education, at least 18 years of age, English as the primary language, and ability to provide informed written consent. Exclusion criteria included a history of opportunistic central nervous system infection, traumatic brain injury (loss of consciousness for 30 minutes or longer), confounding neurological or psychiatric disorders, current severe depressive symptoms (Beck depression inventory-II $\geq$ 29 [17]), self-reported substance use disorder, or contraindications for MRI scanning.

Clinical Characteristics of PWH Participants

For the PWH group, all individuals were on a stable cART regimen for at least 6 months had had a recent viral load <200 copies/mL. Viral load was obtained from either blood samples collected at the research study visit or from the medical evaluations that occurred within 1 month of assessment. Duration of HIV infection and nadir CD4 T-cell counts were obtained from either medical records or self-report; CD4 and CD8 T-cell counts were obtained from medical records within 3 months of the study visit. The central nervous system penetrating effectiveness score, a measure that quantifies how well an antiretroviral drug crosses the blood-brain barrier [18], was calculated for each participant's current cART regimen [19, 20].

Cardiovascular Risk Score

For a subset of participants (PWoH n = 28; PWH n = 85) with available data, we calculated the Framingham 10-year cardiovascular disease risk score [21, 22]. This score incorporates age, sex, systolic blood pressure, hypertension diagnosis and treatment, self-reported smoking status, diagnosis of diabetes, high-density lipoprotein, and total cholesterol.

MRI Acquisition and Processing

The structural/anatomical 3-dimensional T1w and T2w images were acquired sagittally on a high-resolution 3T MR Siemens Tim Trio (Siemens AG) with a 12-channel head coil. For the T1w images, scanning was performed with magnetization-prepared rapid gradient echo (MP-RAGE) sequence with repetition time = 2400 ms, echo time = 3.16 ms, flip angle = 8°, and inversion time = 1000 ms. The T2w scan sequence had repetition time = 3200 ms, echo time = 450 ms, and variable flip angle. Both sequences were configured with matching resolution = $1 \times 1 \times 1$ mm^3 voxels, $256 \times 256 \times 176$ acquisition matrix, and generalized autocalibrating partial parallel acquisition acceleration of 2.

T1w/T2w ratio maps were generated by 3 sequentially executed Human Connectome Project structural pipelines. These pipelines [23] were containerized using the Quantitative Neuroimaging Environment and Toolbox (Qu|Nex) Suite version 0.45.07, which included the Human Connectome Project processing pipelines [23], FreeSurfer version 6.0 [24], FSL version 6.0.1 [25], and Connectome Workbench version 1.3.2 [26]. Briefly, the Human Connectome Project pipeline applied preparatory transformations to the T1w and T2w scans—reduction of the field of view, removal of oblique orientation, brain extraction, and radio frequency field homogeneity correction. This pipeline constructed the white matter and pial surfaces as well as segmented the cortical structures according to the Desikan-Killiany standard atlas in FreeSurfer [27]. A trained technician (AB) inspected the volume and surface images generated by FreeSurfer. The individual midthickness surface was calculated between the white matter and pial surfaces with FreeSurfer default 164 k vertices and 0.9 mm average spacing between them [28]. T1w/T2w ratios from the cortical

ribbon were projected onto the midthickness surface to generate a T1w/T2w ratio map for each participant. A myelin field map was applied to compensate for overestimation in lightly myelinated areas. The T1w/T2w ratio was calculated both globally (average of the whole-cortex T1w/T2w ratio values) and regionally for the 34 cortical regions of interest (ROIs). For the regional analysis, we combined results from both hemispheres for the 34 cortical ROIs.

Statistical Analyses

Demographic variables including age, sex, race, and education were compared between PWH and PWoH using Mann-Whitney U tests for continuous variables and χ^2 tests for categorical variables. Prior to all analyses, the global T1w/T2w value was adjusted for cortical thickness using linear regression. For each ROI, similar regressions were performed for the T1w/T2w ratio by adjusting for the corresponding ROI cortical thickness in the regression. Standardized residuals from these analyses were used as the dependent variables in subsequent analyses.

The global T1w/T2w ratio was compared between PWH and PWoH using an analysis of covariance (ANCOVA) test, with age and sex included as covariates. Similar ANCOVAs were performed for each of the cortical ROIs.

Partial correlation analyses were performed to examine relationships between global T1w/T2w ratios and duration of infection, CNS penetration effectiveness score, nadir CD4 T-cell count, recent CD4 T-cell count, recent CD8 T-cell count, and the CD4/CD8 ratio, after adjusting for age. Linear regression models analyzed relationships between global or ROI T1w/T2w ratios and the Framingham cardiovascular risk score in PWoH and PWH. Finally, regression analyses examined the pattern of change in global T1w/T2w ratios for PWoH and PWH over the lifespan. A false discovery rate method was used to adjust for multiple comparisons for all analyses [29].

RESULTS

Demographics

Demographic and clinical variables are presented for PWoH and PWH participants in Table 1. The groups were well matched with regards to race. However, the PWH were significantly older ($P = .01$), reported a lower degree of education ($P = .01$), and a greater percentage were male ($P < .001$) compared to PWoH. No difference was observed between PWH and PWoH in the Framingham risk score for cardiovascular risk ($P = .17$). Age, education, and sex were included as covariates in subsequent analyses when appropriate.

Global and ROI T1w/T2w Ratios Significantly Differ Between PWoH and PWH

The global T1w/T2w ratio, adjusted for total cortical thickness and demographic variables, significantly differed between PWoH and PWH ($P < .001$; Cohen $d = 0.64$). PWH had significantly lower T1w/T2w values compared to PWoH (Figure 1).

Analyses examining differences in T1w/T2w values for the 34 ROIs identified significantly lower T1w/T2w values within the posterior cingulate cortex ($P < .001$; adjusted P value = .003; Cohen $d = 0.58$), caudal anterior cingulate cortex ($P = .002$; adjusted P value = .02; Cohen $d = 0.52$), and

Table 1. Demographic, Clinical, and Cognitive Characteristics of Persons Without HIV and Persons With HIV

Characteristics	PWoH (n = 120)	PWH (n = 164)	*P* Value
Demographic characteristics			
Age, y, mean (SD)	41.3 (17.1)	47.9 (14.7)	**.01**
Sex, % male	48	79	**<.001**
Race, % African American	59	66	.14
Education, y, mean (SD)	13.8 (2.2)	13.1 (2.7)	**.015**
Framingham 10-y cardiovascular risk score, mean (SD)	13.2 (5.1)	19.2 (13.6)	.17
Current smoker, % yes	27	47	**<.001**
HIV characteristics			
Duration of infection, mo, median (IQR)	NA	196 (114–288)	NA
Duration of cART, mo, median (IQR)	NA	170 (63–237)	NA
Recent CD4 T-cell count, median (IQR)	NA	628 (438–907)	NA
Nadir CD4 T-cell count, median (IQR)	NA	200 (33–333)	NA
Recent CD8 T-cell count, median (IQR)	NA	820 (597–1340)	NA
CD4/CD8 ratio, mean (SD)	NA	0.70 (0.5)	NA
CNS_{PE}, mean (SD)	NA	7.3 (1.3)	NA

Bolded *P* values are significant at $P < .05$.

Abbreviations: cART, combination antiretroviral therapy; CNS_{PE}, central nervous system penetrating effectiveness score; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; PWH, persons with HIV; PWoH, persons without HIV.

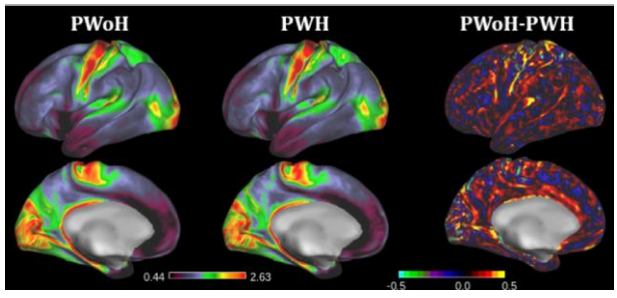

Figure 1. Group average T1w/T2w values in PWoH (left) and PWH (middle), and the group difference (PWoH – PWH) are displayed based on the ratio intensity (right). Higher group averages of T1w/T2w ratios (red in the left and middle images), such as those observed in the motor cortex, are hypothesized to correspond to regions of higher myelination. Overall, PWH exhibit reduced T1w/T2w ratios compared to PWoH (right). Abbreviations: PWH, people with HIV; PWoH, people without HIV; T1w/T2w, T1-weighted/T2-weighted.

insula ($P = .002$; adjusted P value = .02; Cohen $d = 0.61$) for PWH compared to PWoH (Figure 2). There were no ROIs where PWH had a higher T1w/T2w ratio compared to PWoH.

Relationships Between T1w/T2w Values and HIV Disease Variables in PWH

After adjusting for age, T1w/T2w values did not significantly correlate with duration of HIV infection in PWH. T1w/T2w ratios also was not significantly associated with current or nadir CD4 T-cell counts, current CD8 T-cell count, or CD4/CD8 ratio. Regression analyses examining relationships between T1w/T2w ratios and cardiovascular disease risk scores in a subset of participants with available data (PWoH n = 28; PWH n = 85) identified a significant effect of a higher risk score and lower global ($r = -0.25$; $P = .01$) and insula ($r = -0.4$; $P < .001$) T1w/T2w ratios within PWH but not PWoH.

No significant relationship was observed between the global or regional T1w/T2w ratios and duration of ART, current ART regimen, or class of current antiretrovirals. Higher CNS penetration effectiveness scores were correlated with lower T1w/T2w ratios for the caudal anterior cingulate cortex ($r = 0.20$, $P = .008$), posterior cingulate cortex ($r = -0.29$, $P < .001$) (Figure 3), precuneus ($r = -0.25$, $P < .001$), and insula cortex ($r = -0.20$, $P = .01$).

Change in Global T1w/T2w Ratios Across the Lifespan for PWoH and PWH

Regression analyses assessed linear and nonlinear relationships between age and T1w/T2w values for PWoH and PWH. Age was not significantly associated with global T1w/T2w ratios for PWoH ($P = .92$). In contrast, age was linearly associated with the global T1w/T2w ratio ($P < .001$) for PWH, with increasing age associating with lower global T1w/T2w values (Figure 4).

DISCUSSION

The focus of the present study was to evaluate global and regional T1w/T2w ratios between PWoH and PWH. We observed a significant reduction in T1w/T2w values both globally and regionally in PWH compared to PWoH. Anatomical regions with reduced T1w/T2w ratios for PWH included frontal, cingulate, and insular regions, which have previously been shown to be affected by HIV [30]. Although the T1w/T2w ratio was not significantly associated with any known HIV disease metrics, an association was observed with a measure of cardiovascular disease risk and a measure of cART penetration into the CNS. Finally, increasing age was associated with reductions in the T1w/T2w ratio for PWH but not PWoH.

The T1w/T2w ratio was introduced as a measure of myelin concentration throughout the cortex [4]. The simplicity of this metric underlies its utility, as this measure can be easily calculated using T1w and T2w images that are commonly acquired during an MRI session, avoiding the need for long, costly MRI sequences. Additional reported benefits of the T1w/T2w ratio include test-retest reliability, high spatial resolution, and high signal-to-noise ratio that reduces bias of the MR signal, allowing comparison of T1w/T2w values across different sites, scanners, and sequences [4]. The T1w/T2w ratio has a demonstrated ability to differentiate between high-myelinated and low-myelinated cortex regions [31], in addition to differentiating between healthy versus clinical populations [8, 9, 13, 15], and associates with cognitive performance [6]. Importantly, this measure may provide researchers and clinicians with more-specific information about microstructural brain integrity compared to brain volumetrics, cortical thickness, or DTI, which demonstrates low sensitivity to cortical myelin. These features highlight the potential application of this measure to HIV, a disease that continues to be associated with microstructural changes within the white matter despite cART and viral suppression [1, 3].

The results of the current study add to this literature and support the sensitivity of the T1w/T2w ratio in detecting differences between PWoH and PWH who are virologically well controlled. We observed significantly lower global T1w/T2w values in PWH compared to PWoH, as well as regional reductions in cingulate cortices and the insula. Prior work has shown that impairment of the cingulate cortices and their connections are associated with worse cognitive performance and reduced quality of life in HIV-positive populations [32, 33]. Previous studies have also reported volumetric changes in both the cingulate and insula between PWH and PWoH [25]. Our findings accounted for cortical atrophy at each of these regions, suggesting microstructural neurodegenerative changes may still be present in PWH despite virological control. In contrast to our results, one previous study that evaluated the T1w/T2w metric in PWH observed an elevated signal, which was associated with positron emission tomography (PET) inflammatory markers. However, this study was based on a smaller sample of PWH and included individuals who were and were not on cART. Additionally, we observed significant correlations between increasing age and lower T1w/T2w values in PWH that were not observed in PWoH. Prior literature has shown a reduction in the T1w/T2w metric was associated with increased aging [7], and PWH often demonstrate accentuated aging even in virologically suppressed individuals [34, 35].

We did not observe significant relationships between HIV disease metrics and the T1w/T2w ratio. However, lower T1w/T2w values were associated with a higher Framingham risk score and higher medication penetration, quantified by the central nervous system (CNS) penetration effectiveness score. PWH have been reported to be at higher risk for cardiovascular disease that associates with worse neuroimaging metrics of brain integrity [36]. There is some debate as to whether high CNS penetration effectiveness medications are beneficial or deleterious to brain integrity. Several previous studies have

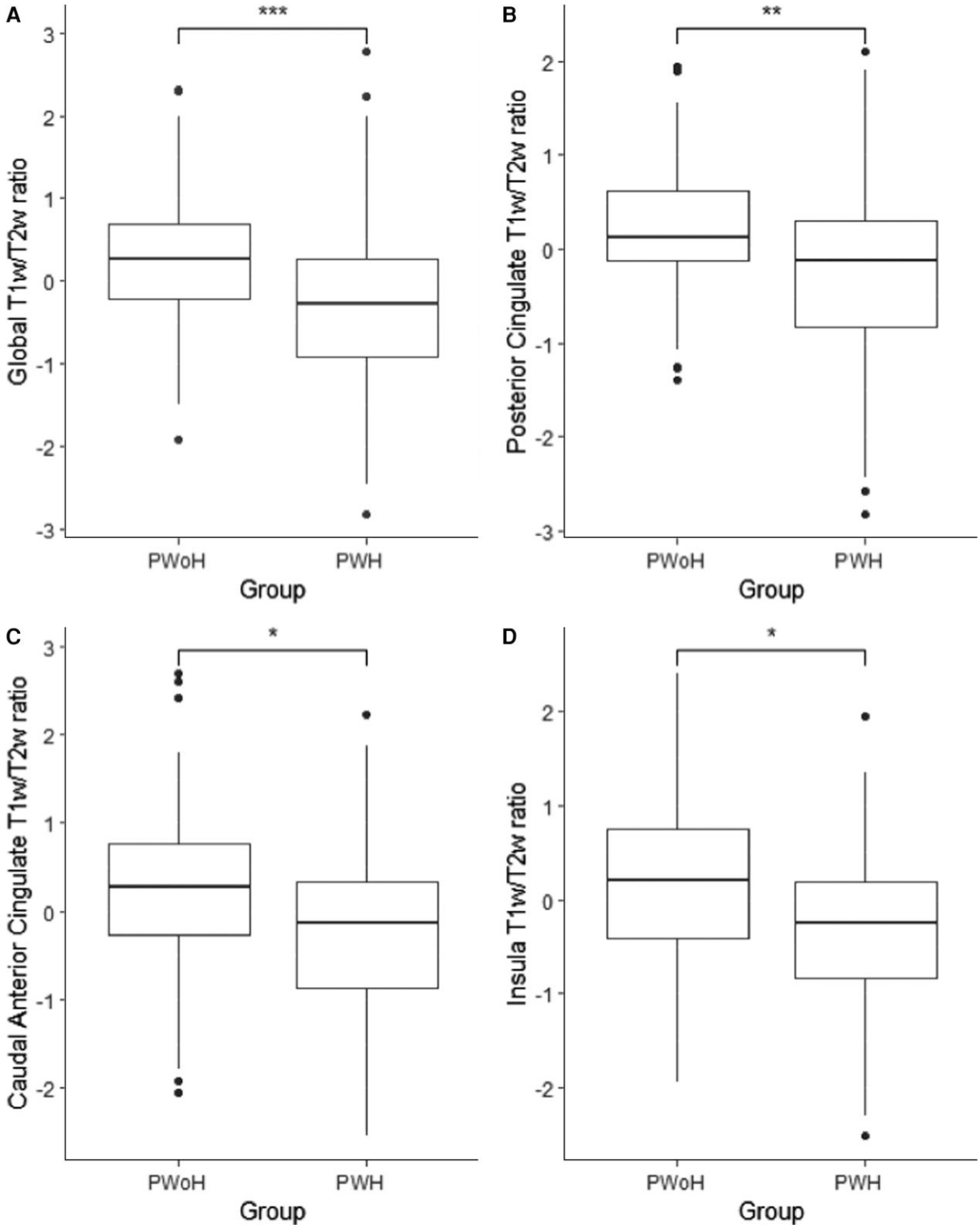

Figure 2. Box plots representing the quartiles (box and whiskers), outliers (circles), the median and 95% confidence interval for the global (*A*) and regional posterior cingulate (*B*), caudate anterior cingulate (*C*), and insula (*D*) T1w/T2w values for PWoH compared to PWH. Significance was determined using the analysis of covariance general linear model. PWH demonstrated significantly lower global and regional T1w/T2w values compared to PWoH. Abbreviations: PWH, people with HIV; PWoH, people without HIV; T1w/T2w, T1-weighted/T2-weighted. $^{*}P < .05$, $^{**}P < .01$, $^{***}P < .001$.

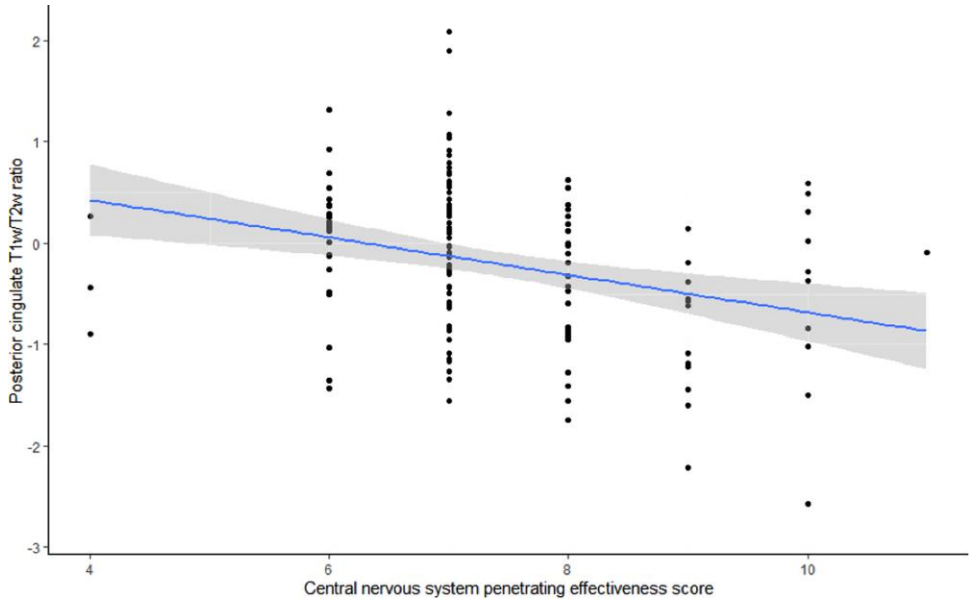

Figure 3. A linear regression was conducted with central nervous system penetrating effectiveness score as a function of the T1w/T2w ratio within the posterior cingulate cortex in people with HIV ($r = -0.29$, $P < .001$). The shaded areas represent the 95% confidence interval. Abbreviation: T1w/T2w, T1-weighted/T2-weighted.

observed no significant effect of CNS penetration effectiveness score on cognition and brain volumes [37, 38]. However, cART medications have been associated with mitochondrial toxicity and oligodendrocyte dysfunction, which may result in loss of myelin and reduced white matter microstructural integrity in PWH [39]. The T1w/T2w ratio may be more sensitive to these subtle changes than more conventional neuroimaging measures such as brain volumes and DTI. Further research with more detailed medication regimen information is needed to clarify this potential relationship.

Our study complements previous results of reduced T1w/T2w signal in inflammatory diseases, such as multiple

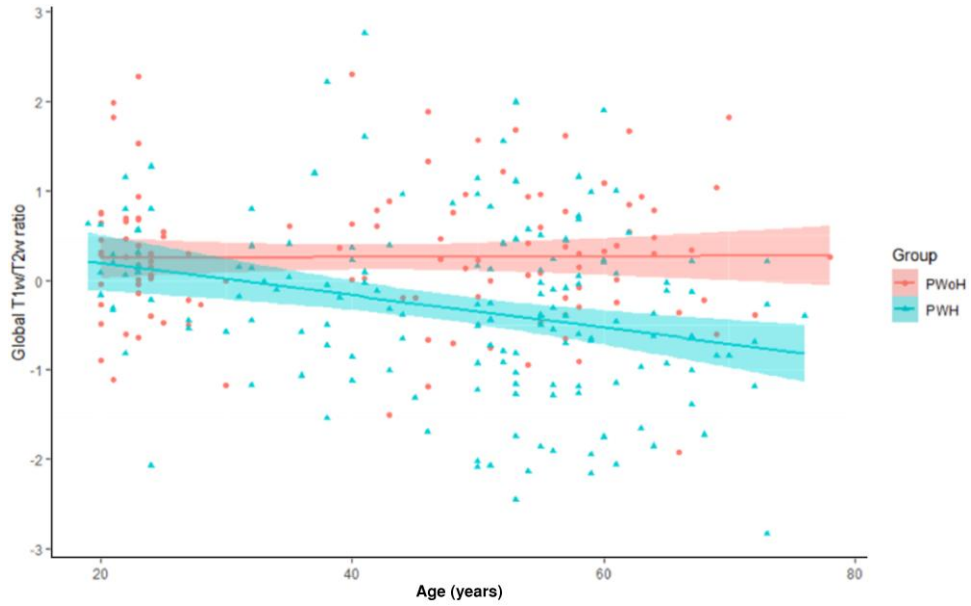

Figure 4. A linear regression was conducted with age as a function of global T1w/T2w ratio for PWoH and PWH. The shaded areas represent the 95% confidence intervals for each group. A significant effect of age was seen for PWH ($P < .001$) but not PWoH ($P = .92$). Abbreviations: PWH, people with HIV; PWoH, people without HIV; T1w/T2w, T1-weighted/T2-weighted.

sclerosis, compared to healthy individuals [8–10]. However, studies demonstrating higher values of T1w/T2w ratios in neurodegenerative diseases such as Alzheimer disease [15] and Parkinson disease [13] suggest that other disease processes, including increased iron accumulation and decreased neuronal density, may alter the T1w/T2w signal [40, 41]. Interestingly, a recent, large study of the T1w/T2w value in multiple clinical phenotypes of multiple sclerosis found both reduced cortical T1w/T2w ratios and increased subcortical T1w/T2w ratios that associated with the differing clinical phenotypes and disease phase or severity [11]. From these data, the authors concluded that the T1w/T2w value may reflect the combination of multiple etiologies, such as demyelination, loss of neuronal density, and iron accumulation. More specifically, at milder stages of disease pathology in the brain, changes in the T1w/T2w ratio may primarily reflect subtle white matter changes while high levels of neurodegeneration and brain pathology may result in other factors affecting this signal in a manner that increases the T1w/T2w ratio. Our sample of PWH that are on cART and virologically well controlled demonstrated a reduction in the T1w/T2w ratio that corresponded with CNS penetration effectiveness. Taken together, these results indicate that the T1w/T2w ratio is likely capturing subtle differences in white matter microstructural integrity that may be due to medications or legacy effects of HIV rather than the virus itself.

There are several limitations to consider with the present study. As noted above, there is some controversy over the anatomical correlate for changes in the T1w/T2w signal and interpretation of this metric in certain cohorts may be challenging due to the presence of other neuropathological causes. The T1w/T2w signal is useful for determining low and high areas of myelination that are affected by age. However, in the presence of pathology, a reduction in the signal can only be attributed to nonspecific myelin damage as multiple sources can influence the overall signal. Consequently, interpretation of the T1w/T2w ratio should be done with caution and with the understanding that other etiologies may influence this measure. Additionally, this study is cross-sectional, and longitudinal data is necessary to aid in understanding whether the relationships observed would be consistent or change over time, as well as to help clarify the observed correlation between age and T1w/T2w values in PWH but not PWoH individuals. AIDS diagnosis was not acquired for some of our PWH and therefore could not be analyzed with the T1w/T2w ratio. With regards to age, we had relatively few participants between the ages of 25 and 45 years, particularly in our PWoH sample, which may have impacted the linear relationship with age observed (vs a nonlinear relationship). To avoid committing a type I error, we were more stringent in our significance criteria for the regional analyses. These statistical strategies are common for neuroimaging analyses but can inflate the potential for committing a type II error. Finally, PWH recruited into the study had well-controlled virus (<200 copies/mL) and were on cART, limiting the ability to examine potential changes in the T1w/T2w ratio in more severe cases.

The T1w/T2w ratio is a relatively novel neuroimaging marker that can be calculated from commonly acquired T1 and T2 MRI scans and may be sensitive to subtle changes in white matter microstructural integrity. In a sample of PWH with well-controlled virus, the T1w/T2w ratio was significantly reduced compared to PWoH, both globally and regionally in the cingulate cortices and insula. Lower T1w/T2w ratios were also associated with increased age and higher cART penetration in the CNS in PWH, highlighting the need for future research to more fully understand these relationships. Overall, the T1w/T2w represents an easily acquired neuroimaging metric that has potential utility in examining subtle microstructural changes to brain integrity in PWH, although more studies are needed to fully determine the pattern of change in T1w/T2w values with neuropathology in diseases.

Notes

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