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Comparison of [^{11}C]-PBR28 binding between persons living with HIV and HIV-uninfected individuals

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Abstract

Objective: Despite combined antiretroviral therapy (cART), neuroinflammation may persist in persons living with HIV (PLWH) and contribute to cognitive impairment in this population. Positron emission tomography (PET) imaging targeting 18kDa translocator protein (TSPO) has been used to localize neuroinflammation. We aimed to use TSPO-PET imaging to evaluate neuroinflammation in PLWH.

Design: Twenty-four virologically suppressed PLWH on cART and thirteen HIV-negative (HIV-) controls completed TSPO-PET imaging using the radiotracer [^{11}C]PBR28. Due to tracer complexity and differing procedures used in previous studies, we employed an expansive methodological approach, using binding potential (BP) and standard uptake value ratio (SUVR) and multiple different reference regions to estimate [^{11}C]PBR28 binding.

Methods: [^{11}C]PBR28 binding was measured in thirty cortical and subcortical regions and compared between PLWH and HIV- controls. Pearson correlation evaluated the association between [^{11}C]PBR28 binding and cognition and clinical measures of HIV.

Results: Analyses conducted using multiple reference regions and measures of tracer uptake revealed no significant differences between [^{11}C]PBR28 binding in PLWH compared to HIV-

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Conflicts of Interest

The authors report no conflicts of interest.

controls. Additionally, [^{11}C]PBR28 binding in PLWH was not significantly associated with clinical measures of HIV or plasma biomarkers of inflammation. [^{11}C]PBR28 binding was not significantly elevated in cognitively impaired PLWH compared to unimpaired PLWH, but there were inverse relationships between cognitive performance (executive and global function) and [^{11}C]PBR28 binding in PLWH.

Conclusions: Our results suggest that neuroinflammation may play a role in cognitive deficits, but overall, neuroinflammatory levels as measured by TSPO PET imaging in PLWH are not significantly different than those seen in HIV- controls.

Keywords

HIV; neuroinflammation; positron emission tomography; 18kDa translocator protein; cognition

INTRODUCTION

The introduction of combined antiretroviral therapy (cART) has significantly improved the prognosis for persons living with HIV (PLWH), with life expectancy approaching that of HIV uninfected (HIV-) individuals[1]. Despite lifesaving advances, an estimated 30%–50% of PLWH develop cognitive impairments, with difficulties observed in learning, memory, and executive function that may disrupt daily living and quality of life[2].

The neuropathology of this impairment remains poorly characterized, but neuroinflammation has been implicated as a key contributor[3]. HIV penetrates the central nervous system (CNS) soon after seroconversion and triggers an immunological response[4]. Even after initiating cART, HIV can continue to reside and replicate in reservoirs in the brain[3]. Possible brain reservoirs of HIV are microglia, which may cause persistent neuroinflammation[3]. Chronic neuroinflammation can lead to neuronal damage and the development of neurocognitive symptoms despite cART.

Plasma and cerebrospinal fluid (CSF) biomarkers are commonly used to evaluate inflammation in PLWH. However, these measures may reflect persistent systemic changes and cannot localize inflammation in the brain. Positron emission tomography (PET) targeting the 18kDa translocator protein (TSPO) has been used to quantify the spatial distribution of neuroinflammation *in vivo*[5]. TSPO is located in the outer mitochondrial membrane of the microglia and is upregulated with microglial activation[5]. TSPO is, therefore, considered a proxy measure of inflammation in the brain and is a target for many PET radiotracers. While the first-generation tracer specific for TSPO, [^{11}C]*R*-PK11195, is still used, this tracer is limited by high nonspecific binding and low blood-brain barrier penetration[5]. Second-generation tracers, such as [^{11}C]DPA-713 and [^{11}C]PBR28, provide improved signal-to-noise ratios and better blood-brain barrier penetration[5]. However, binding affinity of these second-generation tracers is dependent on single nucleotide polymorphism rs6971[6]. Genotype testing must be performed to determine whether an individual is a low-affinity binder (LAB), mixed-affinity binder (MAB), or high-affinity binder (HAB)[6].

Several studies have used TSPO PET imaging to investigate neuroinflammation in PLWH on cART, but with inconsistent results[7]. Although the majority of these studies report higher neuroinflammation in PLWH, the spatial topographies vary among cortical and subcortical regions. Furthermore, mixed findings have been observed in a subset of these TSPO PET studies that have evaluated the relationship between neuroinflammation and cognition. These inconsistencies may be attributed to (1) cohort differences (e.g. inclusion vs. exclusion of PLWH with cognitive impairment), (2) differences in measurements of cognition, (3) tracer differences (e.g. first- vs. second-generation), and/or (4) differences in data analysis (e.g. definition of reference region and quantification of tracer uptake). Overall, previous studies have employed different analysis and processing methods, and conflicting results have been observed with regards to the presence of neuroinflammation in PLWH as measured by TSPO PET imaging.

The aim of this study was to evaluate neuroinflammation in HIV- controls and virologically suppressed PLWH on cART using the TSPO PET radiotracer [11C]PBR28. Since previous similar studies use varying methodological approaches, we employed a few of these different methodologies to examine how our results compare. We also analyzed how neuroinflammation as measured by TSPO PET imaging correlated with plasma biomarkers of neuroinflammation. Finally, since neuroinflammation has been implicated as a contributor to the cognitive impairment seen in PLWH, we also aimed to measure the relationship between neuroinflammation and cognitive performance.

METHODS

Participants

PLWH were recruited from the Washington University School of Medicine (WUSM) Infectious Disease Clinic and the WUSM AIDS Clinical Trial Unit. All were chronically infected (≥1 year), receiving cART for at least 6 months, and virologically suppressed, which is defined by the Department of Health and Human Services as HIV RNA < 200 copies/mL[8]. HIV- controls were also recruited and were tested within 3 months of enrollment to confirm HIV seronegative status. Using self-report and available medical records, participants were included based on the following criteria: age ≥18 years old, negative pregnancy test and not breast feeding if female, minimum of approximately 8 years of education, not currently using benzodiazepines whether prescribed or not (as these medications inhibit TSPO PET binding), have not used anti-inflammatories within approximately the past week, able to undergo a PET and/or magnetic resonance imaging (MRI) scan, able to provide written informed consent. Participants were excluded based on the following criteria: claustrophobia, implanted medical devices (including pacemakers) or conditions that would preclude the individual from completing PET and MRI scans, history of confounding neurological disorders, any Axis I psychiatric disorder that is not well-controlled, inability to provide informed consent. All participants provided informed, written consent, and the study was approved by the WUSM Institutional Review Board.

Blood samples were collected and tested for TSPO affinity genotype before PET imaging using a TaqMan assay on demand C_2512465_20 (Applied Biosystems, Waltham, MA)[9].

Three PLWH and two HIV- control LABs were excluded to avoid unnecessary exposure to radiation.

For PLWH, current plasma CD4 cell count and plasma HIV RNA levels were measured from the blood sample. After three PLWH with high viral loads were excluded (HIV RNA = 2784, 23622, and 45086 copies/mL), twenty-four virologically suppressed HAB and MAB PLWH were included in the study. Nadir CD4 cell count, the difference between current and nadir CD4 (ΔCD4), duration of HIV infection, and the CNS penetration-effectiveness (CPE) score of cART were obtained for each PLWH. Within a subset of 12 PLWH, inflammatory biomarkers in the plasma were also obtained using previously described methods, including soluble CD163 (sCD163), soluble CD14 (sCD14), and neopterin[10]. Relative percentages of monocyte subpopulations (classical: CD14+CD16−; inflammatory: CD14+CD16+; non-classical: CD14-CD16+) and CD4+ and CD8+ T cells were calculated. CD4/CD8 ratio was also calculated as the percentage of CD4+ T cells divided by the percentage of CD8+ T cells. Additional details describing acquisition methods are included in the Supplemental Digital Content.

Neuropsychological assessment

Within 1 year (±0.62 years) of [^{11}C]PBR28 PET imaging, participants completed neurocognitive testing using measures sensitive to HIV[11]. Neurocognitive tests (detailed in Supplemental Digital Content) assessed the following cognitive domains: learning/memory, psychomotor/processing speed, and executive function[12].

Raw test scores were converted to standardized z-scores using published normative data, adjusted for age, sex, race, and education where applicable[13]. A composite z-score for global cognition was defined by the average of the domain z-scores. A binary classification of “cognitively impaired” was defined as having a composite z-score < −2 SD in one domain or < −1 SD in two domains[13].

[^{11}C]PBR28 processing

All participants underwent magnetic resonance imaging (MRI) and PET imaging, the specifics of which are detailed in the Supplemental Digital Content. Dynamic PET images were processed using an established processing pipeline (PET Unified Pipeline; https://github.com/ysu001/PUP). Partial-volume correction was performed using a regional spread function technique[14]. The T1-weighted MRIs were segmented into regions of interest (ROIs) using Freesurfer v5.3 (Martinos Center for Biomedical Imaging, Charlestown, MA). We selected 30 cortical and subcortical ROIs to analyze: white and grey matter of the four major lobes, right and left hemisphere white matter, total cortical grey matter, and specific gray matter and subcortical regions based on previous TSPO PET studies of HIV (Supplemental Table 2)[15]. Regional time-activity curves (TACs) were generated for each ROI using co-registered T1 segmentation. To measure [^{11}C]PBR28 binding, we estimated the binding potential (BP_{ND}) from the regional TAC data during the 30–90-minute interval, when the rate of [^{11}C]PBR28 uptake has been shown to reach steady-state[16]. BP_{ND} was estimated using Logan graphical analysis with a predefined reference region[17]. As a secondary

analysis, we calculated standard uptake value ratios (SUVRs) using regional TAC data from the 60–90-minute interval[18].

In PET analysis, the effects of nonspecific binding are offset by normalizing each ROI to a reference region that historically and quantitatively exhibits low tracer binding. However, the literature remains conflicted regarding the choice of a stable reference region for TSPO PET tracers. The cerebellum has often been used as the reference region of choice for other PET tracers and has previously been used in TSPO PET studies for other disease conditions[18]. Alternate reference regions previously utilized in PET imaging studies of HIV include cortical and white matter regions[19–21]. Due to lack of consensus, three pseudo-reference regions were used to calculate BP_{ND} and SUVR: the cerebellum cortex (CB), total gray matter (GM), and unsegmented white matter (UWM). UWM is a white matter region defined by Freesurfer as white matter >5 mm from the cortical ribbon and had relatively low binding in both PLWH and HIV- controls.

Statistical analysis

Statistical analyses were performed using RStudio v1.1.463. All BP_{ND} and SUVR values were adjusted using linear regression with genotype as a categorical variable to account for its effect on [^{11}C]PBR28 binding affinity. Group regional differences were evaluated with a two-sample Student's T-test to compare [^{11}C]PBR28 binding in PLWH and HIV- control participants. We also used a two-sample Student's T-test to compare [^{11}C]PBR28 binding between cognitively unimpaired and impaired PLWH. In addition to these comparisons, we calculated Hedge's g to estimate the effect size of HIV status and impairment status on [^{11}C]PBR28 binding. Finally, Pearson correlation was performed to evaluate the associations among [^{11}C]PBR28 binding, cognitive domain, global z-scores, and laboratory measures. Additionally, within a subset of PLWH participants, the correlation between [^{11}C]PBR28 binding and measures of plasma inflammatory markers, the percentage of monocyte subsets, and the CD4/CD8T cell ratio were evaluated. For both the comparison and correlation analyses, the BP_{ND} values were adjusted for TSPO genotype. To correct for multiple comparisons, the Benjamini-Hochberg procedure was used to adjust the *P* values for false discovery rate (FDR), and the Hedge's g effect sizes were adjusted using the Bonferroni correction method.

RESULTS

Demographics and neuropsychological performance

Twenty-four PLWH and 13 HIV- controls completed imaging. Demographics and clinical HIV laboratory measures are presented in Table 1, and cognitive performance z-scores are presented in Table 2. All HIV- controls and 23 PLWH completed the full neuropsychological battery (Supplemental Table 1). No significant differences were evident between PLWH and HIV- controls on domain z-scores or overall global z-score (all $P > 0.05$).

[^{11}C]PBR28 binding in PLWH compared to HIV- controls

Using GM, UWM, and CB as reference regions, BP_{ND} was calculated and compared between HIV- controls and PLWH. For all three reference regions, no significant differences

in BP_{ND} were observed between HIV- controls and PLWH (Fig, 1, Supplemental Fig. 1A, Supplemental Table 2). Due to the homogeneity of these results and the relatively low binding in UWM for both HIV- controls and PLWH participants, UWM was selected as the primary pseudo-reference region.

As a secondary analysis, we compared SUVR between HIV- controls and PLWH. No significant differences were observed between the two groups (Supplemental Fig. 1B). All subsequent analyses therefore utilized BP_{UWM} to measure [^{11}C]PBR28 binding. However, in all cases, regardless of methodology, no significant differences between HIV- controls and PLWH were observed. We also did not measure an effect of HIV status on tracer binding (Hedge's $g < 0.8$).

Correlations with clinical variables for PLWH

Within PLWH, current and nadir CD4 cell count and DCD4 did not correlate with BP_{UWM} in any of the 30 regions. BP_{UWM} also did not correspond to duration of infection or CPE score of cART (data not shown). Furthermore, there was no significant relationship between BP_{UWM} and any of the plasma inflammatory biomarkers (sCD163, sCD14, neopterin) or the percentage of inflammatory cells (CD4/CD8 ratio, CD14-CD16+, CD14+CD16+, CD14+CD16−).

Correlation with cognitive performance

Among PLWH participants, worse executive function was inversely correlated with BP_{UWM} in the parietal cortex ($P_{FDR} < 0.001$), total cerebral cortex ($P_{FDR} = 0.013$), caudal middle frontal cortex ($P_{FDR} = 0.019$), frontal cortex ($P_{FDR} = 0.021$), thalamus ($P_{FDR} = 0.022$), and occipital cortex ($P_{FDR} = 0.033$) (Supplemental Fig. 2). A significant correlation was also observed between lower global cognitive z-score and increased BP_{UWM} in the parietal cortex ($P_{FDR} = 0.005$) for PLWH (Supplemental Fig. 2). No significant correlations were found in HIV- controls.

PLWH were further stratified as unimpaired (n = 16) or impaired (n = 7). However, BP_{UWM} was not significantly elevated in impaired PLWH compared to unimpaired PLWH (Supplemental Fig. 3). There was also no significant relationship between BP_{UWM} and neuropsychological z-scores in either unimpaired or impaired PLWH ($P_{FDR} > 0.05$). However, we did observe a large effect of impairment status on BP_{UWM} in the parietal cortex (g = 1.28; CI = [−0.42, 2.99]), thalamus (g = 1.01; CI = [−0.65, 2.67]), right hemisphere cerebral white matter (g = 1.01; CI = [−0.65, 2.66]), caudal middle frontal cortex (g = 1.00; CI = [−0.66, 2.66]), total cerebral cortex (g = 0.92; CI = [−0.72, 2.56]), occipital cortex (g = 0.85; CI = [−0.78, 2.48]), and frontal cortex (g = 0.82; CI = [−0.81, 2.44]).

DISCUSSION

This study used [^{11}C]PBR28 PET imaging to assess neuroinflammation in a well-characterized cohort of older, virologically suppressed PLWH on stable cART and demographically similar HIV- controls. The results of our analyses using multiple reference regions and measures of tracer uptake consistently showed no significant differences in [^{11}C]PBR28 binding between PLWH and HIV- controls or show any effect of HIV status on

tracer binding. Additionally, [^{11}C]PBR28 binding in the PLWH participants was not significantly associated with clinical measures of HIV, such as current and nadir CD4 cell count, duration of infection, or CPE score of cART, nor was there any correlation between tracer binding and plasma biomarkers of inflammation. We observed a relationship between increased [^{11}C]PBR28 binding and cognition in PLWH, specifically for global and executive function, but binding was not significantly elevated in impaired PLWH compared to unimpaired PLWH. Our results suggest that neuroinflammation, as measured by [^{11}C]PBR28, may play a role in cognitive deficits seen in PLWH but, overall, is not significantly elevated in virologically suppressed PLWH on cART.

Previous studies have used biofluid biomarkers to evaluate neuroinflammation in virologically suppressed PLWH and HIV- controls. Some of these studies observed increased inflammation in PLWH, but a number of them did not measure differences between PLWH and HIV- controls[22,23]. In one study, Gisslén and colleagues utilized soluble triggering receptor expressed on myeloid cells (sTREM2) as a correlate of microglial activation. This marker potentially measures a similar mechanism of neuroinflammation to that captured by TSPO[24]. No differences were observed for sTREM2 between virologically suppressed PLWH on cART and HIV- controls. Other studies have also measured CSF levels of sCD14 and sCD163, markers of activated macrophages, and found similar levels for virologically suppressed PLWH compared to HIV- controls[25,26]. Congruent findings also have been observed with other CSF biomarkers, reflecting alternative mechanisms within the inflammatory cascade, including chitinase-3-like protein 1 (YKL-40) and neopterin. In many of these cases, virologically suppressed PLWH had inflammatory levels comparable to those of HIV- controls[27–30]. The current findings support our observations that neuroinflammation is not significantly elevated in virologically suppressed PLWH on stable cART.

Evaluations of neuroinflammation using TSPO PET imaging in PLWH also have shown mixed results[7]. In some studies, neuroinflammation was not elevated in both PLWH and animal models of HIV[31]. Similar to our study, Wiley and colleagues compared PLWH on cART with HIV- controls using the PET tracer [^{11}C]*R*-PK11195 and did not observe significant differences between the groups[32]. Although other studies have observed elevated neuroinflammation in PLWH, there is no consistent overlap between affected regions (Table 3)[19–21,25,32]. As previously stated, these studies used a variety of methods to process and analyze the PET data, which may account for conflicting results. To address these inconsistencies, we implemented several previously well-described approaches to analyze the data with regard to uptake (BP and SUVR) and reference region (GM, UWM, and CB). Varying results may be due differences in the cohorts evaluated. For instance, studies have differed on inclusion or exclusion of virologically uncontrolled PLWH and on accounting for genotype. The degree of impairment of studies' cohorts also varied, with some studies excluding impaired participants and others including both unimpaired and impaired participants (Table 3). Previous TSPO PET imaging studies often compared younger participants (Table 3). In the current study, we compared a larger cohort of older PLWH to comparable HIV- controls. Differences between our study and others may also be attributed to immunosenescence, the deterioration of the immune system as a result of aging[26]. Future studies focused on differentiating the potential effects of aging on neuroinflammation in PLWH should be performed.

Clinical measures of HIV, such as current CD4 cell count, can provide insight into disease severity and cART effectiveness. Our results did not show a relationship between levels of neuroinflammation and clinical measures of HIV. These findings are supported by previous PET and biomarker studies and suggest that current levels of inflammation are not affected by previous immunological history (as assessed by nadir CD4, ΔCD4, and duration of infection) (Table 3)[22,25,32–34]. However, only suppressed PLWH were included. Future studies evaluating PLWH on cART with virological failure are necessary to thoroughly assess the relationship between these clinical measures and neuroinflammation.

Neuroinflammation has been associated with worse cognition in neurodegenerative diseases, including HIV[5]. Within PLWH, we observed an inverse relationship between cognitive performance and neuroinflammation, specifically within the global and executive function domains. Additionally, the specific ROIs in which binding was most significantly correlated with poorer executive functioning were in the frontal and parietal lobes, regions commonly associated with executive functioning[35]. Findings from a few studies using plasma and CSF biomarkers of inflammation have also observed a relationship with poorer executive function and global cognition[22,36,37]. Previous TSPO PET studies also observed correlations between these two cognitive domains and increased tracer binding in PLWH, but the regions where these correlations were found differed (Table 3)[20,25,38]. These correlations were also based on a limited amount of data and may have been driven by a few outlying participants or noise. Within PLWH, there were no significant differences in BP_{UWM} for impaired compared to unimpaired individuals. However, we observed a strong effect ($g > 0.8$) for impairment status on tracer binding suggesting a larger of number of impaired PLWH is needed. Within HIV- controls, no significant relationship was observed between neuroinflammation and cognitive performance. Overall, these results suggest that neuroinflammation may play a role in cognitive impairment but is not significantly elevated in PLWH compared to HIV- controls.

Our study had a number of limitations. Although this study was the largest TSPO-PET study of PLWH, the sample size was still relatively small and may not have been sufficiently powered to detect significant differences. The cost of PET scanning limited our ability to recruit a larger sample and restricted our study to a cross-sectional analysis. A longitudinal analysis could evaluate neuroinflammatory changes in virologically suppressed PLWH. We also did not collect blood plasma tracer concentrations but, instead, used reference regions to normalize tracer binding among individuals. However, previous studies in PLWH have used reference regions. Recent concerns have also been raised about using TSPO as a marker of neuroinflammation. Not only is TSPO expression not exclusive to microglia, but its function is not well understood[39]. Our preliminary results did not show any significant relationship between [^{11}C]PBR28 binding and plasma levels of inflammatory markers, percentage of monocyte subpopulations, or CD4/CD8 ratio. Although these biomarkers were measured in blood plasma rather than CSF, our results suggest that these two approaches are measuring different aspects of the inflammatory process. In order to best interpret the results of a TSPO PET study, a better understanding the role of TSPO in the inflammatory process is necessary. Finally, prior studies have disputed whether upregulation of TSPO actually correlates with increased neuroinflammation in humans[40]. Recent efforts have focused on developing alternative neuroinflammatory PET tracers that will also eliminate the genetic

dependency of binding affinity[41]. The TSPO PET tracer [^{11}C]PBR28 was used because a more reliable alternative is not yet widely available.

In summary, this study employed an expansive methodological approach to assess neuroinflammation between PLWH and HIV- controls. Neuroinflammation as measured by [^{11}C]PBR28 PET imaging was not elevated in chronically infected PLWH who were virologically suppressed due to cART. A relationship was observed between cognition and [^{11}C]PBR28 binding within PLWH, suggesting an inflammatory effect on executive performance. However, no differences were seen between unimpaired and impaired PLWH. Overall, this study suggests that PLWH who adhere to stable treatment regimens have neuroinflammatory levels comparable to healthy HIV- controls.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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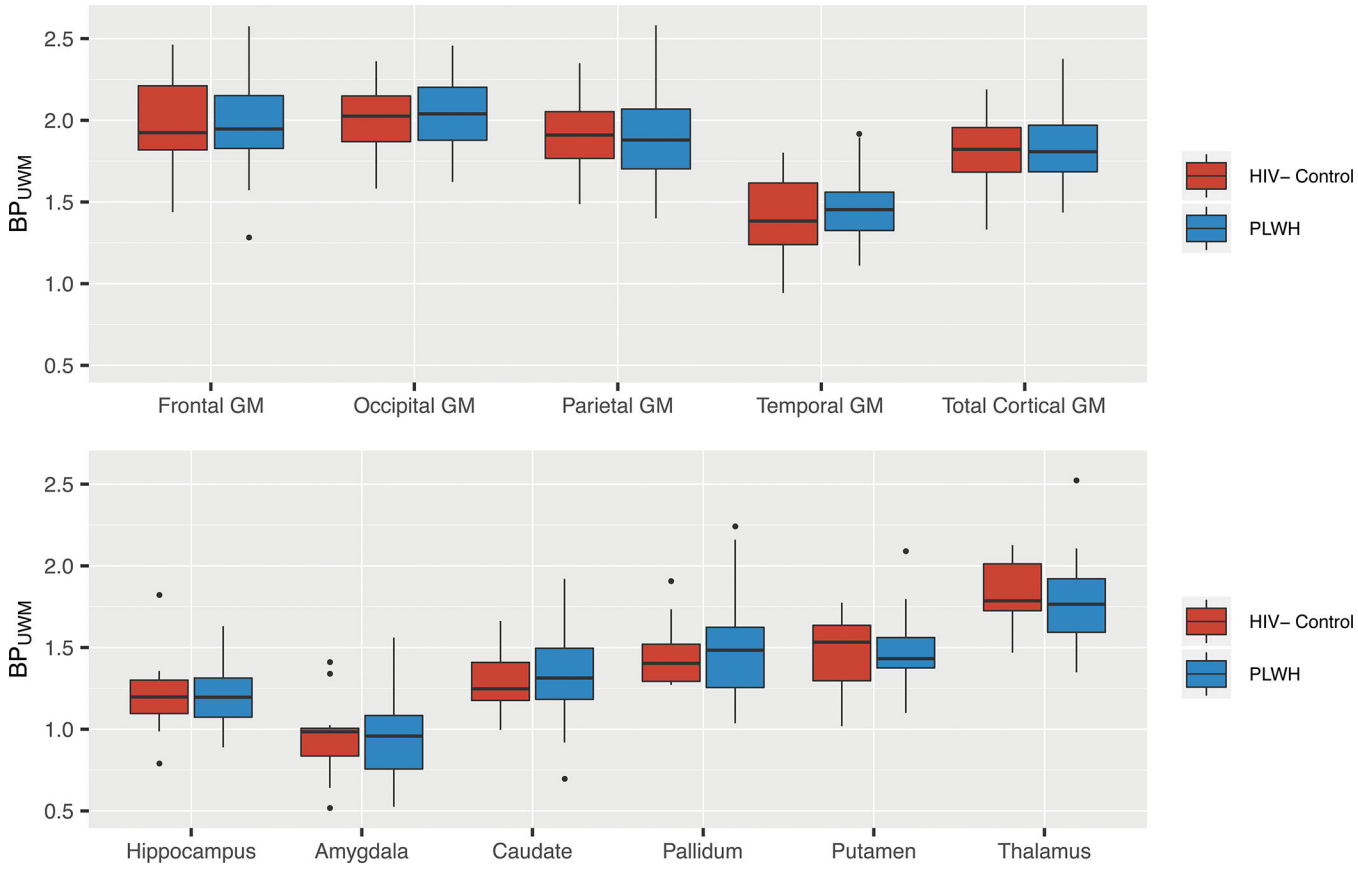

Fig. 1.

Comparison between persons living with HIV (PLWH) and HIV-uninfected (HIV-) controls for [^{11}C]PBR28 binding potential (BP) normalized to unsegmented white matter (UWM) and adjusted for translocator protein genotype. Top panel reflects cortical regions of interest, and bottom panel reflects subcortical regions of interest.

Abbreviations: GM, gray matter

Table 1.

Demographics of HIV-uninfected (HIV-) controls and persons living with HIV (PLWH)

	HIV- Controls	PLWH	*P* value
N	13 (7 HAB, 6 MAB)	24 (13 HAB, 11 MAB)	—
Age (years ± SD)	58.5 ± 6.6	56.8 ± 6.0	0.451
Sex (% Male)	69	75	0.715
Body Mass Index (mean ± SD)	29.1 ± 7.5	26.3 ± 5.4	0.199
Race (% African American)	69	67	0.692
Education (years ± SD)	13.4 ± 2.5	14.0 ± 2.8	0.596
Current CD4 cell count (median, IQR)	—	514 (386.0–636.5)	—
Nadir CD4 cell count (median, IQR)	—	117 (20.75–344.75)	—
Duration of infection (years ± SD)	—	18.3 ± 8.0	—

P values calculated from two-tailed t-test

Abbreviations: HAB, high-affinity-binder; MAB, mixed-affinity binder; SD, standard deviation; IQR, interquartile range.

Table 2

Neurocognitive domain performance in HIV-uninfected (HIV-) controls and persons living with HIV (PLWH)

Neurocognitive domain z-scores (± SD)	HIV- Controls	PLWH	*P* value
Learning/Memory	−0.25 ± 0.84	−0.84 ± 1.04	0.090
Executive Function	−0.03 ± 0.71	−0.38 ± 0.72	0.167
Psychomotor	0.09 ± 0.69	−0.02 ± 0.70	0.652
Global	−0.03 ± 0.59	−0.33 ± 0.64	0.171

P values calculated from two-tailed t-test

Abbreviations: SD, standard deviation

Table 3.

Summary of current and previous TSPO PET imaging studies in PLWH

	Current Study	Hammoud et al. (2005)	Wiley et al. (2006)	Garvey et al. (2014)	Vera et al. (2016)	Coughlin et al. (2014) [a]	Rubin et al. (2018) [a]
Participants (age, male %)	24 PLWH (57 yrs, 75%) 13 HIV- controls (59 yrs, 69%)	10 PLWH (45 yrs, 100%) 5 HIV- controls (41 yrs, 80%)	12 PLWH (49 yrs, N/A) 5 HIV- controls (40 yrs, N/A)	7 PLWH (48 yrs, N/A) 9 HIV- controls (31 yrs, N/A)	12 PLWH (42 yrs, 100%) 10 HIV- controls (41 yrs, 100%)	20 PLWH [b] (46 yrs, N/A) 11 HIV- controls [b] (39 yrs, N/A)	21 PLWH (48 yrs, 81%) N/A
PLWH cognitive status	16 unimpaired 7 impaired	5 unimpaired 5 impaired	6 unimpaired 6 impaired	7 unimpaired	12 unimpaired	12 unimpaired 8 impaired	13 unimpaired 8 impaired
TSPO PET radiotracer	[^{11}C]PBR28	[^{11}C]R-PK11195	[^{11}C]R-PK11195	[^{11}C]R-PK11195	[^{11}C]PBR28	[^{11}C]DPA-713	[^{11}C]DPA-713
HIV- controls vs. PLWH	No significant difference	Thalamus, putamen, cerebellum, frontal GM, and occipital GM	No significant difference	Targeted ROI analysis: No significant difference Voxel analysis: CC, anterior and posterior cingulate, temporal GM and frontal GM	Parietal lobe, occipital lobe, and globus pallidus	Supramarginal GM, temporal GM, and WM [b]	N/A
Unimpaired vs. Impaired PLWH	No significant difference	No significant difference	No significant difference	N/A	N/A	Frontal cortex	N/A
PLWH ~ Current CD4	No significant correlation	N/A	No significant correlation	N/A	N/A	N/A	N/A
PLWH ~ Nadir CD4	No significant correlation	N/A	N/A	No significant correlation	No significant correlation	N/A	N/A
PLWH ~ Duration of infection	No significant correlation	N/A	N/A	No significant correlation	No significant correlation	N/A	N/A
PLWH ~ Cognitive performance	Executive function: Parietal GM and total cerebral GM Global: Parietal GM	N/A	N/A	Executive function: Anterior and posterior cingulate and CC	Memory and verbal learning: Hippocampus and thalamus Global: Hippocampus, right amygdala, and thalamus	N/A	Learning and Memory: Cerebellum, temporal GM, middle frontal gyrus, occipital GM, parietal GM, and thalamus Psychomotor, Processing Speed: Occipital GM and hippocampus Executive function: Frontal GM and hippocampus

[a] Rubin et al. used same pool of PLWH participant data used in Coughlin et al.

[b]Results of comparison between only high- and mixed-affinity persons living with HIV (PLWH) and HIV-uninfected (HIV-) controls, excluding 3 low-affinity PLWH and 1 lowaffinity HIV- control

Abbreviations: TSPO, translocator protein; yrs, years; GM, gray matter; ROI, region of interest; CC, corpus callosum WM, white matter