HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2024 July 15.

Published in final edited form as:

AIDS. 2023 July 15; 37(9): 1419–1424. doi:10.1097/QAD.0000000000003572.

Pilot imaging of the colony stimulating factor 1 receptor in the brains of virally-suppressed individuals with HIV

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Abstract

Objective: Neuroimmune activation is a putative driver of cognitive impairment in people with HIV (PWH), even in the age of modern antiretroviral therapy. Nevertheless, imaging of the microglial marker, the 18kDa translocator protein (TSPO), with positron emission tomography (PET) in treated PWH has yielded inconclusive findings. One potential reason for the varied TSPO results is a lack of cell-type specificity of the TSPO target.

Design: [^{11}C]CPPC is a radiotracer for use with PET to image the colony stimulating factor 1 receptor (CSF1R). The CSF1R is expressed on microglia and central nervous system macrophages, with little expression on other cell types. We used [^{11}C]CPPC PET in virally-

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Authors' contributions

LR, YD, AGH, MP, and JC jointly developed the concept of the manuscript. LR, YD, SES, RO, CH, KJ, WL, RV, RD, JS, HF, DH, AWH, RFD, AGH, MP, and JC each contributed to data acquisition. LR, YD, WL, and RD led the analysis, with AGH, MP, and JC contributing to interpretation of the findings. All authors were involved in the writing and proof reading of the manuscript.

List of Supplemental Digital Content

Supplemental Digital Content 1.doc

Competing interests

Under a license agreement between D&D Pharmatech and the Johns Hopkins University, the University, AGH, and MGP are entitled to royalty distributions related to the technology described in the study. MGP is a founder of and holds equity in D&D Pharmatech. He also is a paid consultant to the company. AGH is a paid consultant to the company. As the spouse of MGP, JMC shares his disclosures. This arrangement has been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies.

suppressed- (VS)-PWH and HIV-uninfected individuals to estimate the effect sizes of higher CSF1R in the brains of VS-PWH.

Methods: Sixteen VS-PWH and 15 HIV-uninfected individuals completed [^{11}C]CPPC PET. [^{11}C]CPPC binding (V_T) in nine regions was estimated using a one-tissue compartmental model with a metabolite-corrected arterial input function, and compared between groups.

Results: Regional [^{11}C]CPPC V_T did not significantly differ between groups after age- and sex- adjustment (unstandardized beta coefficient [B]=1.84, standard error [SE]=1.18, P=0.13). The effect size was moderate (Cohen's d=0.56, 95%confidence interval [CI] −0.16, 1.28), with strongest trend of higher V_T in VS-PWH in striatum and parietal cortex (each P=0.04; Cohen's d=0.71 and 0.72 respectively).

Conclusions: Group difference in [^{11}C]CPPC V_T was not observed between VS-PWH and HIV-uninfected individuals in this pilot, although the observed effect sizes suggest the study was underpowered to detect regional group differences in binding.

Keywords

HIV; microglia; CSF1R; cognitive impairment; PET; brain imaging

Introduction

Chronic neuroimmune activation is a putative driver of cognitive impairment in people with HIV (PWH) [1]. Within virally-suppressed (VS)-PWH, several viral and immune processes may contribute to biotypes of cognitive impairment, each marked by characteristic, immune signatures [2]. Detection of neuroimmune biomarkers in PWH promises to inform our understanding of the immune mechanisms underlying cognitive impairment and guide immune-modulating therapies [1, 2].

Imaging the translocator protein 18 kDa (TSPO) has been pursued to study the response of microglia in cognitive disorders, including in PWH [3]. In health, microglial TSPO is low and is upregulated in expression after brain injury or in neuroinflammation. Across several studies, TSPO imaging with positron emission tomography (PET) failed to consistently reveal high TSPO on activated microglia in VS-PWH compared to HIV-uninfected individuals [3]. Nevertheless, high TSPO associates with low cognitive performance within VS-PWH [4–7]. Inconsistent group differences in TSPO levels across prior studies may be due to limitations in TSPO as a stand-alone marker of the microglial response. For example, TSPO expression may be upregulated by non-microglial cells such as astrocytes over the disease course and/or aging [8, 9]. Conversely, heterogeneity in the pathophysiology of cognitive impairment in PWH may account for the lack of group-level detection of microglial activation. Imaging other non-TSPO neuroimmune markers in VS-PWH may aid in the study of the microglial contribution to cognitive outcomes.

The colony stimulating factor 1 receptor (CSF1R) is expressed primarily by microglia and central nervous system (CNS) macrophages in the brain, and is essential to microglial survival and proliferation [10]. High CSF1R was reported in human postmortem cases of neurodegeneration [11, 12] including VS-PWH [13]. High CSF1R was also found in

cortex of a simian immunodeficiency virus (SIV)-infected model of HIV, including virally-suppressed animals [14]. [^{11}C]CPPC was developed for detecting the CSF1R with PET [15] and demonstrated pharmacokinetics that facilitate regional binding estimates [16].

Here we used [^{11}C]CPPC PET in a cross-sectional study of VS-PWH and HIV-uninfected individuals to test for high CSF1R in VS-PWH.

Methods

Human Participants

The study was approved by the Johns Hopkins Investigational Review Board and Radiation Safety Committees. Each participant provided written, informed consent. The study was conducted between May 2021 and September 2022. Individuals within 30–80 years old completed a screening visit with laboratory testing. Participants were excluded if they had: 1) unstable health in the past year, 2) acute illness in the past month, 3) lack of English fluency, 4) recent (within two weeks) use of an anti-inflammatory medication, 5) nicotine or recreational substance use in the past six months (cannabis was exclusionary), or 6) contraindication to magnetic resonance imaging (MRI) or PET with an arterial line. PWH were also excluded if labs revealed detectable viral load (>20 copies/ml).

Clinical and Cognitive Assessments

Cognition was assessed using an iPad-based platform, BrainBaseline Assessment of Cognition and Everyday Functioning (Clinical Ink, Inc; Supplemental Methods). Plasma was isolated from whole blood that was collected prior to each PET. Fourteen participants completed an optional lumbar puncture for cerebrospinal fluid (CSF). Biofluids were stored at −80°C before immune analyte analysis (Supplemental Methods).

Brain Imaging

[^{11}C]CPPC PET—[^{11}C]CPPC was synthesized as previously described [17] in compliance with standard good manufacturing practice. PET data were acquired on a High Resolution Research Tomograph (Siemens Healthcare, Knoxville, TN) [18].

A thermoplastic facemask was molded to the face for head fixation. A radial artery catheter was inserted for manual blood sampling at ~30 time points over the course of the 90 min emission scan [16], with plasma radioactivity counted in a cross-calibrated gamma well-counter (PerkinElmer 2480 WIZARD2 Automatic Gamma Counter, Shelton, CT). At 5, 10, 20, 30, 40, 60 and 90 min post-injection (p.i.), the fraction of parent [^{11}C]CPPC in plasma was measured using a modified column-switching HPLC method [15]. The metabolite-corrected time activity curve (TAC) was then generated with PMOD software (v3.7, PMOD Technologies Ltd, Zurich, Switzerland) using the parent [^{11}C]CPPC at each time and the total plasma TACs [16].

MRI Acquisition and Regions of Interest—Structural T1-weighted Magnetization-Prepared Rapid Gradient-Echo was acquired at 3 Tesla (0.75 × 0.75 × 0.8 mm voxel size) on either a Siemens MAGNETOM (Prisma, Malvern, PA, USA) or

Philips Achieva scanner (Best, Netherlands). The FreeSurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) was used to segment each MRI. Nine regions of interest (ROIs) were selected: thalamus, striatum, hippocampus, as well as cerebellar, temporal, occipital, cingulate, frontal, and parietal cortices. Total cortical gray matter (GM) was defined for testing the association between [^{11}C]CPPC binding in GM and neuropsychological performance.

PET Kinetic Analysis—PET data were reconstructed and corrected as previously published [16, 19]. PMOD v3.7 (Zurich) was used for processing of [^{11}C]CPPC PET and MRI data. PET data were rigidly transformed into MR space by co-registering each of the 30 motion-corrected PET frames to the T1-weighted MRI image. The primary binding outcome was total distribution volume, V_T [20]. V_T was derived by applying a one tissue compartment model (1TCM) to 90 min time-activity data with a metabolite-corrected arterial input function. Since V_T is influenced by atrophy, the Muller-Gartner algorithm [21] was applied for partial volume correction (PVC) of the PET data prior to V_T estimation. V_T estimates from images without PVC were secondary binding outcomes.

Statistics

Regional V_T values were compared between groups (VS-PWH, HIV-uninfected individuals) using a linear mixed model with repeated measures in SAS (Version 9.4, SAS Institute Inc., Cary, NC). We modeled the V_T values from the nine ROIs based on their relationship to between-subject factors, with primary predictors of group, an index variable for brain region, and the two-way interaction. Significance was set at $P<0.05$ for this single mixed model analysis. A priori estimate of effect size was not available in this first-in-patient study. Effect size (Cohen's *d*) for each region was calculated.

Relationships between [^{11}C]CPPC GM V_T and a) cognitive performance and b) circulating (plasma, CSF) immune markers in VS-PWH were assessed using partial correlations. Age and biological sex were included as covariates in all analyses due to each factor associating with regional [^{11}C]CPPC V_T in the total sample (age: $r=0.48$, $P=0.006$; sex: $t=-2.21$, $P=0.03$). Group differences in circulating immune markers were tested using Quade's non-parametric analysis of covariance, adjusting for sex and age.

Results

Participants

VS-PWH (n=16) and HIV-uninfected individuals (n=15) were similar in sociodemographic factors and injected activity, except that VS-PWH had attained fewer years of formal schooling than HIV-uninfected individuals (Table 1). The groups did not differ cognitively except that VS-PWH had lower Stroop performance. VS-PWH had higher plasma IL-6 compared to HIV-uninfected individuals (Supplemental Table 1), with no group differences in other circulating immune markers.

Brain Imaging

VS-PWH had smaller age- and sex-adjusted brain region volumes (mean[M]=57.68, standard error [SE]=1.58) compared to HIV-uninfected individuals (M=63.51, SE=1.63) (unstandardized beta coefficient[B]=−5.83, SE=2.27, *P*=0.02, *d*=−0.92, 95%confidence interval[CI] −1.66, −0.18). The magnitude of the group difference depended on region, *P*=0.001. The largest group differences in brain volume were in frontal (B=−19.77, SE=3.53, *P*<0.001; *d*=−2.02, 95%CI −2.88, −1.15), parietal (B=−8.34, SE=3.53, *P*=0.02, *d*=−0.85, 95%CI −1.59, −0.12), and temporal cortices (B=−8.04, SE=3.53, *P*=0.02; *d*=−0.82, 95%CI −1.55, −0.09).

Age and biological sex were associated with regional [^{11}C]CPPC V_T (B=0.21, SE=0.07, *P*=0.009; B=2.93, SE=1.25, *P*=0.03). In age- and sex-adjusted analyses, VS-PWH did not differ in regional [^{11}C]CPPC V_T (M=23.55; SE=0.82) versus HIV-uninfected individuals (M=21.71; SE=0.85)(B=1.84, SE=1.18, *P*=0.13); albeit the effect size was moderate (Cohen's *d*=0.56, 95%confidence interval [CI] −0.16, 1.28). The pattern of group differences was similar across regions (*P*=0.25; Fig. 1; see also Supplemental Table 2, which lists regional group comparisons of [^{11}C]CPPC V_T values). However, the direction of higher binding in VS-PWH was strongest in the striatum and parietal cortex (each *P*=0.04; Cohen's *d*=0.71 and 0.72 respectively). No group difference was observed using regional V_T values derived from data without correction for atrophy (PVC) (B=1.32, SE=1.02, *P*=0.20).

Among VS-PWH, higher [^{11}C]CPPC V_T in GM associated with better processing speed (Digit Symbol: *r*=0.70, *P*=0.008) and showed a trend association with poorer behavioral inhibition (Stroop: *r*=0.50, *P*=0.07) after adjusting for age and biological sex. There were no other associations between [^{11}C]CPPC V_T in GM and cognition.

Discussion

This is the first evaluation of [^{11}C]CPPC PET to evaluate for high CSF1R on activated microglia and CNS macrophages in a clinical population. Early studies using PET to detect another marker of activated microglia, TSPO, yielded inconsistent findings in VS-PWH compared to HIV-uninfected individuals [3]. The current [^{11}C]CPPC PET data do not support a marked increase in the CSF1R on microglia in the brains of VS-PWH over HIV-uninfected individuals. However, the group comparison of regional mean [^{11}C]CPPC binding revealed a non-significant trend of higher V_T in striatum and parietal cortex of VS-PWH over HIV-uninfected individuals, with a medium standardized mean difference (Cohen's *d* =0.71 and 0.72 respectively). The medium effect size suggests that the pilot study was underpowered to detect a group difference, and that approximately 31 individuals per group are required to examine regional difference in striatum or parietal cortex with at least 80% power. Beyond the limited sample size, VS-PWH had unimpaired cognitive performance and showed higher plasma IL-6 alone, without other high inflammatory markers relative to the HIV-uninfected individuals. Future studies using [^{11}C]CPPC PET may benefit from enriching the VS-PWH for cognitive impairment and/or peripheral inflammation that may result from and drive microglial activation respectively [22].

The primary outcome was regional V_T derived from PET radioactivity data that had been adjusted for regional brain atrophy. This adjustment was supported by observed, smaller regional volumes and published faster rate of brain atrophy in VS-PWH compared to HIV-uninfected individuals after age- and biological sex-adjustment [23]. However, a risk of employing this adjustment is an introduction of more noise or variation in the data. Secondary comparison of regional V_T values derived from PET data without adjustment for atrophy also revealed a non-significant trend of higher V_T across regions in VS-PWH compared to HIV-uninfected individuals.

The found relationship between higher [^{11}C]CPPC binding in GM and better processing speed counters the model of detrimental microglial effect on cognition in VS-PWH. High occipital GM TSPO, which marks microglial activation, associated with lower processing speed in VS-PWH in prior work [6]. Across studies that employ multiple neuropsychological tests, discrepant findings may arise from high false discovery rate. However, a comprehensive neuropsychological battery is suited best to capture the cognitive heterogeneity in VS-PWH [24]. Efforts to determine best practices for neuropsychological assessments and statistics in study of HIV-associated complications are a high priority [24].

Analyses were adjusted for a found association between age and [^{11}C]CPPC V_T. We also found that males had higher binding compared to females. Within PWH, cognitive correlates of neuroinflammation may differ by sex, with a found association between central immune markers and processing speed in males and memory impairment in females [25]. Future study of the microglial response in VS-PWH would benefit from study of interaction between effects of HIV-seropositivity and aging or biological sex on microglial response and cognitive outcomes.

Conclusions

Pilot [^{11}C]CPPC PET data do not support robust microglial activation and proliferation in VS-PWH compared to HIV-uninfected individuals. However, the observed medium effect sizes of higher [^{11}C]CPPC binding in striatum and parietal cortex of VS-PWH suggest that the study was underpowered to detect group differences in some regions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors would like to thank Dr. Scott H. Mittman (Johns Hopkins Department of Anesthesiology), as well as the technologists and managerial staff at the Johns Hopkins PET Center for assistance in the acquisition of these human PET data. The authors will also like to thank the following individuals for their contributions in the development of the iPad-based platform, BrainBaseline Assessment of Cognition and Everyday Functioning (BRACE, Clinical Ink, Inc): Isabel Bagheri (BRACE Design), Katelyn McDonald (multimedia design), and Yefei He, PhD, Dan Amato, and Michael Merickel (software engineering and design).

Funding:

This work was supported by the National Institutes of Health [MH125278, EB024495].

Data Availability Statement:

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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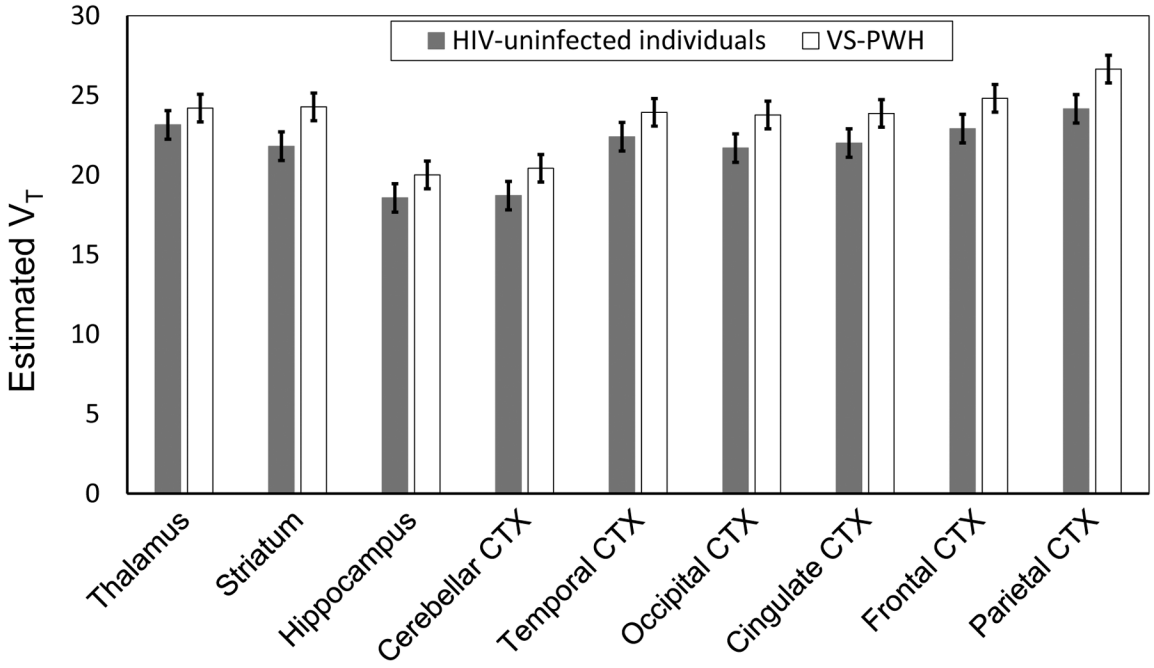

Figure 1. There were no group differences in age-adjusted regional [^{11}C]CPPC PET total distribution volume (V_T) values between virally-suppressed PWH and HIV-uninfected individuals.

Estimated V_T is in units of mL cm^{-3} adjusted for age in years and biological sex. Error bars reflect standard error.

Table 1.

Demographic and cognitive characteristics of the virally-suppressed PWH and uninfected individuals

	PWH (n=16)	HIV-uninfected individuals (n=15)	*P*-value	Cohen's *d*
Sociodemographics				
Age, M (SD)	59.4 (6.9)	55.5 (9.2)	0.20	
Years of Education, M (SD)	13.3 (2.4)	15.4 (2.1)	0.02	
Male, n (%)	11 (69)	9 (60)	0.61	
Race, n (%)			0.44	
Black	9 (56)	6 (40)		
White	7 (44)	8 (53)		
Asian	0 (0)	1 (7)		
[^{11}C]CPPC at time of injection				
Molar Activity (GBq/μmol), M (SD)	307.55 (133.23)	267.06 (77.58)	0.31	
Injected dose of radioactivity (MBq), M (SD)	678.00 (19.73)	677.94 (41.11)	1.00	
Injected mass (μg), M (SD)	1.11 (0.59)	1.10 (0.27)	0.97	
Cognitive Test Performance, M (SE) †				
Trail Making Test (time to completion [sec])				
Part A	18.44 (2.32)	15.98 (2.41)	0.50	0.26
Part B	47.57 (3.16)	38.72 (3.28)	0.08	0.70
Digit Symbol Substitution				
Number correct	26.81 (2.69)	33.41 (2.79)	0.12	−0.61
Stroop Test (reaction time cost [ms])				
Trial 3 (Interference) - Time 2	379.53 (64.76)	120.59 (69.93)	0.01	0.98
Go/No-Go				
Mean reaction time in correct go trials (ms)	653.98 (32.48)	569.03 (36.58)	0.11	0.62
go/no-go accuracy	0.95 (0.01)	0.96 (0.01)	0.72	0.25
n-back				
Overall performance accuracy	0.54 (0.20)	0.73 (0.19)	0.21	0.25
Spatial Working Memory Task				
Overall performance accuracy	0.73 (0.04)	0.79 (0.05)	0.40	0.34
Visual Spatial Learning				
Total correct across trials 1–3	5.29 (1.14)	7.81 (1.29)	0.19	0.53
Visual Search (reaction time cost [ms])				
Mean on conjunction – feature, 4 item display	271.99 (62.78)	193.59 (70.71)	0.45	0.30
Mean on conjunction – feature, 12 item display	960.72 (89.32)	725.26 (100.60)	0.11	0.63
Flanker (reaction time cost [ms])				
Mean on Incongruent - Congruent Trials	52.34 (15.98)	35.89 (16.59)	0.51	0.26
Finger Tapping (total taps)				
Dominant hand	125.55 (13.12)	152.91 (13.66)	0.19	−0.52
Non-dominant hand	117.35 (11.12)	144.83 (11.58)	0.14	−0.59

PWH=people with HIV; M=mean; ms=milliseconds; s=seconds; SD=standard deviation; SE=standard error;

[†]Adjusted for age, years of education, biological sex, and race. *P*-values from comparison using student's t test or chi-square test as appropriate except for comparison of cognitive performance that were assessed using analysis of covariance.