HHS Public Access

Author manuscript

AIDS. Author manuscript; available in PMC 2026 February 01.

Published in final edited form as:

AIDS. 2025 February 01; 39(2): 133–142. doi:10.1097/QAD.0000000000004034.

Imaging the translocator protein 18 kDa within cognitive control and declarative memory circuits in virally-suppressed people with HIV

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Abstract

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Authors' contributions

LR, PMM, YD and JC jointly developed the concept of the manuscript. LR, PMM, YD, SES, RO, HN, HL, ARS, SPR, WGL, IM, RD, EFS, KAW, JS, YW, AWH, WBM, MK, RFD, SGK, AB, MGP, and JC each contributed to data acquisition. LR, PMM, YD, WL, RD, EFS, and JC led the analysis and interpretation of these data. All authors were involved in the writing and proofreading of the manuscript.

Competing interests

None

Objectives: Virally-suppressed people with HIV (VS-PWH) show heterogeneity in patterns of cognitive dysfunction. To better understand the relationship between the neuroimmune response and cognition, we used positron emission tomography (PET) to image the translocator protein 18 kDa (TSPO). The study examined HIV-serostatus differences in TSPO as well as associations between regional TSPO and select cognitive processes defined using the Research Domain Criteria (RDoC) framework.

Design: Cross-sectional investigation in VS-PWH (n=25) versus HIV-uninfected individuals (n=18) of cognitive control and declarative memory, as well as [^{11}C]DPA-713 PET measures of TSPO within cognitive control and declarative memory regions of interest.

Methods: Group differences in [^{11}C]DPA-713 binding (V_T) in cognitive control or declarative memory regions were examined using linear mixed models. Tests of associations between factor-derived cognitive system measures and PET measures were performed, controlling for TSPO genotype.

Results: There were no group differences in any of the four factor-derived cognitive system measures. VS-PWH had higher log [^{11}C]DPA-713 V_T across cognitive control regions(unstandardized beta coefficient reflecting mean difference [B]=0.23, SE=0.11, 95% confidence interval [CI] 0.01, 0.45, *P*=0.04) and declarative memory regions (B=0.24, SE=0.11, 95%CI 0.02, 0.45, *P*=0.03). Higher log [^{11}C]DPA-713 V_T in cognitive control regions related to poorer cognitive control in each group, and to worse self-reported cognitive performance in VS-PWH. Log [^{11}C]DPA-713 V_T in each declarative memory region did not associate with measured declarative memory.

Conclusions: A localized neuroimmune response marked by high TSPO in brain regions that subserve cognitive control may contribute to poorer cognitive control in VS-PWH.

Keywords

HIV; TSPO; [^{11}C]DPA-713; cognitive control; declarative memory; cognition; PET imaging

Introduction

Even with the consistent use of antiretroviral therapy (ART), cognitive complications can persist among virally suppressed people with HIV (VS-PWH). Cross-sectional and longitudinal assessments reveal deficits in attention/working memory, declarative memory, and/or executive function.[1–8] Varied research approaches account for the heterogeneity in cognitive function in HIV by testing for subtypes of cognitive patterns. For example, a recent study in VS-PWH revealed patterns characterized primarily by declines in verbal fluency, executive function, declarative memory or motor skills over a 6-month follow-up, with approximately equal numbers of individuals in each group.[9] Yet, there is limited understanding of the factors that contribute to the heterogeneity of cognitive dysfunction in VS-PWH.

The variables that affect cognitive function in VS-PWH are numerous, and may involve circulating inflammatory signals that persist in spite of viral suppression.[10–12] Recent investigations support a working model wherein peripheral immune signals exert influence

across the blood-brain barrier and on glia (microglia, astrocytes), with resulting shifts in glial cell populations and functional states, as well as detrimental effect on neural circuits critical for cognitive function. The translocator protein 18 kDa (TSPO) is a well-studied protein that marks the regional density of glial cells (microglia, astrocytes), peripheral macrophages, and endothelial cells in the human brain.[13, 14] Higher TSPO captured with positron emission tomography (PET) may serve as a signal of glial cell proliferation in the setting of an acute or chronic immune stimulus. To that end, TSPO PET has been applied to study the immune contribution to numerous neurologic conditions.[15] For example, in early-onset Alzheimer's disease (AD), a distribution of high TSPO was selectively found in only AD-affected regions that co-localized with higher tau burden, and a correlation was found between higher TSPO in the AD-relevant regions and lower cognitive performance within early-onset AD[16]. The high TSPO in human brain does not necessarily signal a detrimental neuroimmune response[13, 14] and much remains unknown about the functional significance of human variants in the *TSPO* gene.[17] Therefore, testing for the hypothesized relationship between higher TSPO along affected neural circuits and worse disease-associated behavior(s) subserved by those regions will aid the interpretation of high TSPO as a marker of a disease-relevant immune response within each condition.

TSPO PEThas included the use of second generation radiotracers ([^{11}C]DPA-713, [^{11}C]PBR28) that have higher binding specificity for the TSPO target over that of the original radiotracer, [^{11}C]PK11195. Collectively, *in vivo* PET data using [^{11}C]DPA-713 or [^{11}C]PBR28 in VS-PWH suggest that higher TSPO within frontal, prefrontal, parietal or cingulate cortices may associate with lower performance across a range of cognitive domains including executive function and verbal memory, among others.[18, 19] Similarly, [^{11}C]PBR28 PET revealed a pattern of higher TSPO in the declarative memory region of hippocampus that correlated with low declarative memory performance,[20] although this same relationship was not found in another study using [^{11}C]DPA-713 PET.[19]

Rigorous examination of the factors contributing to the heterogeneity in cognitive function in VS-PWH can benefit from use of the NIMH Research Domain Criteria (RDoC) framework, which is designed specifically to address the heterogeneity in key dimensions of human function, including cognition.[21, 22] Through this framework, performance is not evaluated solely in terms of standard cut-offs marking deviation from "normal" cognitive function in each domain (e.g., executive function, memory) but instead studied across the full spectrum of performance in each discrete construct. Each cognitive construct of interest can be understood best through data collection, in parallel, across multiple levels of analysis (genetic, molecular, and cell to self-report, behavior, and paradigms). One of the dimensional constructs is cognitive control that is defined as "a system that modulates the operation of other cognitive and emotional systems, in the service of goal-directed behavior, when prepotent modes of responding are not adequate to meet the demands of the current context."[22] Cognitive control relies on the function of dorsal anterior cingulate cortex (dACC), lateral prefrontal cortex (lPFC), and inferior parietal lobe, and includes the subconstructs of goal selection and updating, response selection and inhibition, and performance monitoring.[23] Another RDoC cognitive construct, declarative memory, relies on function of the hippocampus and prefrontal cortex (PFC), and includes encoding, storage and retrieval of facts and events.

Here we aimed to determine if the neuroimmune response marked by higher regional TSPO associates with lower performance in RDoC-defined cognitive constructs in VS-PWH. We hypothesized that, in cognitive control and declarative memory regions and relative to HIV-uninfected controls, VS-PWH would show a pattern of higher TSPO, indicative of altered neuroimmune response in these regions. We further hypothesized that TSPO in cognitive control and declarative memory regions would associate with the behavioral and self-report measures of cognitive control and declarative memory.

Methods

Human Participants

The present study (IRB00196989) was approved by the Johns Hopkins Institutional Review Board and Radiation Drug Research Committee. The study was conducted between April 2021 and March 2023. Volunteers were recruited from the Washington, DC and Baltimore sites of the Multicenter AIDS Cohort Study (MACS)/ Women's Interagency HIV Study (WIHS) Combined Cohort Study (MWCCS), and the Johns Hopkins Clinical Outcomes Core Cohort. Eligible participants entered the **I**maging **M**echanisms in **P**eople with HIV **A**ffected by **C**NS Dysfunction despite **T**reatment (IMPACT) study, a longitudinal investigation focused on the brain correlates of RDoC cognitive processes in VS-PWH. Cross-sectional baseline data from the first year of IMPACT were collected from both VS-PWH and HIV-uninfected individuals, of whom a subset (n=43) participated in an optional [^{11}C]DPA-713 PET scan to image the TSPO target. Each participant in the optional [^{11}C]DPA-713 PET portion underwent testing for the rs6971 polymorphism in the *TSPO* gene.[24] This polymorphism results in three distinct genotypes that have effect on the binding affinity of [^{11}C]DPA-713: C/C (high affinity binding), C/T (mixed affinity binding), or T/T (low affinity binding).

Entry criteria included capacity to perform written informed consent, age between 30–70 years, fluency in English, ability to travel to Johns Hopkins Hospital, and viral suppression defined as <200 copies/mL on screening blood testing. Exclusion criteria included: 1) contraindication to magnetic resonance imaging (MRI) or PET with an arterial line, 2) history of psychosis, 3) current untreated hypertension, diabetes, or other unstable medical condition, 4) head injury with loss of consciousness in the past year, 5) history of substance misuse in the past six months (allowing for nicotine and cannabis, evaluated on screening assessments and urine toxicology), and, for the optional [^{11}C]DPA-713 PET scan, 6) low affinity (T/T) TSPO binding genotype on single nucleotide polymorphism (rs6971) *TSPO* genotyping.[24]

RDoC assessments

Each participant completed a battery of both objective and subjective, self-report assessments, designed to assess cognitive control and declarative memory using the NIMH RDoC framework (Table 1). Cognitive control paradigms consisted of the Eriksen Flanker and Go/No-go tests. The declarative memory paradigms included the Buschke Selective Reminding Task [25–28] and Behavioral Pattern Separation Task-Object (BPS-O) [29, 30]. All measures except the Buschke Selective Reminding Task were administered

via computerized format loaded on either a a) Microsoft Surface Pro model (Microsoft Corporation, Redmond, WA, USA) 1796 using Windows 10 Pro (Go/No-go; BPS-O)[29, 30] or b) 6th generation Apple iPad (Apple, Inc. Cupertino, CA, USA) version 17.3.1 (Brain Baseline Assessment of Cognition and Everyday functioning[5] that included the Eriksen Flanker test). The Buschke Selective Reminding Task [25–28] was administered verbally with a trained test administrator. Further details about the administration of each test can be found in the Supplemental Methods.

Self-report assessments of cognitive control included the Behavior Rating Inventory of Executive Function (BRIEF)[31], which consists of three subscales focused on ability to inhibit (control impulses), shift (transition between activities; flexibility in problem solving), and monitor (assess own performance). Other self-report assessments included the Barratt Impulsiveness Scale[32] to assess impulsiveness, and the Cognitive Failures Questionnaire (CFQ) distractibility subscale,[33, 34] a measure of everyday mistakes. Subjective declarative memory was measured using the forgetfulness subscale from the CFQ.[33, 34] Higher scores on each of these measures indicates greater subjective impairment or difficulty.

Brain Imaging

MRI Acquisition and Regions of Interest—A whole brain, structural T1-weighted Magnetization-Prepared Rapid Gradient-Echo (MPRAGE) sequence was acquired at 3 Tesla (0.75 × 0.75 × 0.8 mm voxel size) on an Achieva scanner (Philips Inc., Best, Netherlands). MRI data was processed using the FreeSurfer image analysis suite to delineate the bilateral, three-dimensional volume for each of five *a priori* brain regions of interest (ROIs). ROIs included those involved in cognitive control [dACC, lPFC, inferior parietal lobe] or declarative memory [hippocampus, PFC] neural circuits. Total intracranial volume was also estimated for use in the group comparison of ROI volumes. Specifically, we examined group differences in ROI volumes adjusting for intracranial volume.

[^{11}C]DPA-713 PET—[^{11}C]DPA-713 was synthesized as previously published[35] in compliance with standard current good manufacturing practice and with 100% radiochemical purity at each synthesis. [^{11}C]DPA-713 was delivered by slow, intravenous injection at the beginning of 90 minutes of continuous emission data collection, and after acquisition of the six-minute transmission scan. PET data were acquired on a brain-dedicated High Resolution Research Tomograph (Siemens Healthineers, Knoxville, TN, USA), with a fitted thermoplastic facemask for head fixation.[36] Arterial blood sampling occurred at ~30 time points over the course of the emission scan.[37] Plasma radioactivity was counted in a cross-calibrated gamma well-counter (PerkinElmer 2480 WIZARD2 Automatic Gamma Counter, Shelton, CT, USA). At 5, 10, 20, 30, 40, 60 and 90 minutes post-injection, the fraction of parent [^{11}C]DPA-713 in plasma was measured as outlined in published work.[38] The metabolite-corrected arterial input function was then generated with PMOD software (v3.7, PMOD Technologies Ltd, Zurich, Switzerland) using the parent fraction of [^{11}C]DPA-713 at each time point and the total plasma time-activity curve.[37]

PET Kinetic Analysis—PET data were reconstructed and corrected as previously published.[37, 39] PMOD v3.7 (Zurich) was used for image data processing. 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 regional total distribution volume, V_T,[40] derived by using Logan graphical analysis, applied to regional time-activity curves with the metabolite-corrected arterial input function. Regional [^{11}C]DPA-713 V_T values (in units of mL cm^{-3}) were derived from images without partial volume correction (PVC), which is a correction applied to account for regional atrophy. [^{11}C]DPA-713 V_T estimates were also derived from images where PVC was applied,[41] and were evaluated as secondary outcomes.

Statistics

Regional [^{11}C]DPA-713 V_T estimates (see Supplemental Table 1 for raw values) were log transformed to normalize the distributions. Group differences in regional log [^{11}C]DPA-713 V_T values were examined using two linear mixed models with repeated measures (one testing for group differences in log [^{11}C]DPA-713 V_T values from the three cognitive control ROIs, and one model testing for group differences in log [^{11}C]DPA-713 V_T values from the two declarative memory ROIs) (SAS Version 9.4, SAS Institute Inc., Cary, NC). Variables in each model included: Group (VS-PWH, HIV-uninfected individuals), an index variable for brain region, TSPO binding genotype (C/C: high affinity binder and C/T: mixed affinity binder), all two-way interactions, and the three-way interaction. Significance was set at $P<0.05$. Within each group, the relationship between log [^{11}C]DPA-713 V_T in cognitive control or declarative memory ROIs and cognition were assessed using partial correlations, with TSPO genotype as a covariate. To reduce the number of outcomes (paradigm, self-report) used across the assessments of cognitive control and declarative memory, we conducted principal components factor analysis with varimax rotation in the total sample and tested for an association between the factor scores and the log [^{11}C]DPA-713 V_T values in cognitive control and declarative memory ROIs. The Benjamini-Hochberg procedure was applied to control for the false discovery rate for the partial correlations.

Results

Participants

VS-PWH (n=25) and HIV-uninfected individuals (n=18) were similar in sociodemographic factors and injected [^{11}C]DPA-713 (Table 2). Twenty-five participants (16 VS-PWH, 9 HIV-uninfected individuals) were of high TSPO binding affinity genotype and 18 had mixed TSPO binding affinity genotype (9 VS-PWH, 9 HIV-uninfected controls). On average, the groups were 57.6 years of age (SD=9.62), had 14.4 years of education (SD=2.18), showed average reading scores (Wide Range Achievement Test-3 reading subtest, mean scaled score=104.33, SD=13.45), were primarily male (65%) and primarily black (54%). Mental health was on average within normal range (mean Patient Health Questionnaire-9 scale score=3.43, SD=4.47; mean General Anxiety Disorder-7 scale score=2.50, SD=3.30).

Behavioral Measures

Four factor scores were identified (Table 3), including *Factor 1:* self-reported cognitive symptom burden (higher scores mark more symptoms), *Factor 2*: verbal memory (higher scores mark higher performance), *Factor 3*: pattern separation and completion (higher

scores mark lower performance in pattern separation) and *Factor 4*: behavioral measures of cognitive control (higher scores mark poorer cognitive control). The groups did not differ in cognitive control or declarative memory factor scores or in self-reported cognitive function (Supplemental Table 2).

Structural MRI Measures

On MRI, there were no group differences in the volumes of cognitive control or declarative memory ROIs after adjusting for total intracranial volume (Supplemental Table 3).

[^{11}C]DPA-713 in cognitive control regions

In TSPO genotype-adjusted analyses, VS-PWH had significantly higher log [^{11}C]DPA-713 V_T across cognitive control ROIs (mean[M] =1.30; standard error[SE]=0.07) compared to HIV-uninfected individuals (M =1.06; SE=0.08) (unstandardized beta coefficient reflecting mean difference [B]=0.23, SE=0.11, 95%confidence interval [CI] 0.01, 0.45, P=0.04) (Figure 1 left). The magnitude of the group difference in log [^{11}C]DPA-713 V_T was similarly high across cognitive control ROIs (P=0.69). The three-way interaction between group, ROI, and TSPO genotype was not significant (P=0.23, Supplemental Table 4). The same patterns were observed using log[^{11}C]DPA-713 V_T values derived from data with PVC, with higher log [^{11}C]DPA-713 V_T across all cognitive control ROIs in VS-PWH (M=1.53, SE=0.07) compared to HIV-uninfected individuals (M=1.28, SE=0.08) (B =0.24, SE=0.11, 95%CI 0.02, 0.46, P=0.03*)*.

[^{11}C]DPA-713 in declarative memory regions

VS-PWH had significantly higher log [^{11}C]DPA-713 V_T across declarative memory ROIs (M=1.23, SE=0.07) compared to HIV-uninfected individuals (M=0.99, SE=0.08) after TSPO genotype adjustment (B =0.24, SE=0.11, 95%CI 0.02, 0.45, P=0.03*)*. The magnitude of the group difference in log [^{11}C]DPA-713 V_T was similar across declarative memory regions (P=0.85; Figure 1 right). The three-way interaction between group, ROI, and TSPO genotype was not significant (P=0.91, Supplemental Table 4). The same patterns were observed using log [^{11}C]DPA-713 V_T values derived from data with PVC: Higher log [^{11}C]DPA-713 V_T was observed in VS-PWH across declarative memory ROIs (M=1.41; SE=0.07) compared to HIV-uninfected individuals (M=1.16; SE=0.08) (B=0.25, SE=0.11, 95% CI 0.03, 0.47, P=0.02).

Associations between [^{11}C]DPA-713 PET imaging and RDoC assessments

Figure 2A provides a heatmap of the partial correlations observed between log [^{11}C]DPA-713 V_T values in cognitive control ROIs and relevant cognitive factor scores, adjusted for rs6971 genotype. Among VS-PWH or HIV-uninfected individuals, lower performance in cognitive control (Factor 4) was associated with higher log [^{11}C]DPA-713 V_T in lPFC (VS-PWH: r=0.45, P=0.03; Controls: r=0.53, P=0.03) and inferior parietal lobe (VS-PWH: r=0.41, P=0.04; Controls: r=0.51, P=0.04). Within VS-PWH, greater self-reported cognitive symptom burden (Factor 1) associated with higher log [^{11}C]DPA-713 V_T in each of the cognitive control ROIs (dACC: r=0.45, P=0.03; lPFC: r=0.44, P=0.03; inferior parietal lobe: r=0.46, P=0.02).

Figure 2B provides heatmap of the partial correlations observed between log [^{11}C]DPA-713 V_T in declarative memory ROIs and relevant cognitive factor scores, adjusted for rs6971 genotype. Within each group, performance in verbal memory (Factor 2) or pattern separation and completion (Factor 3) was not associated with the log [^{11}C]DPA-713 V_T values in either declarative memory ROI (PFC, hippocampus). Greater self-reported cognitive symptom burden (Factor 4) associated with higher log [^{11}C]DPA-713 V_T in the PFC among VS-PWH (r=0.45, P=0.03), but not among HIV-uninfected individuals (r=−0.14, P=0.59).

Discussion

Using PET imaging and the RDoC framework, this study found higher TSPO, a marker of the neuroimmune response, in the brains of VS-PWH relative to HIV-uninfected individuals within *a priori* regions that subserve cognitive control or declarative memory. Our findings are consistent with most[20, 42, 43], but not all[18] studies demonstrating higher regional TSPO in VS-PWH compared to HIV-uninfected controls. Here we focused on relatively smaller regional hubs relevant to functioning of the specific neural circuits governing cognitive control (dACC, lPFC, inferior parietal lobe) or declarative memory (hippocampus, PFC). With respect to cognitive control regions, two prior studies reported that higher TSPO in similar but larger regions of ACC and frontal cortex of VS-PWH may associate with lower performance in cognitive control.[18, 19] With respect to declarative memory, some[20], but not all studies,[19] demonstrate that higher TSPO in the hippocampus of VS-PWH is associated with lower declarative memory performance.

Although the groups did not differ in cognitive control and declarative memory performance, higher TSPO in the lPFC and inferior parietal lobe regions that subserve cognitive control associated with lower performance in cognitive control within VS-PWH or HIV-uninfected individuals. Those findings suggest that higher neuroimmune response in lPFC and inferior parietal lobe is tied more closely to the tasks of cognitive control (Go/No-go, Flanker) than high TSPO in the dACC region. Future work may benefit from adding tests focused on performance monitoring, the subconstruct of cognitive control that reflects more closely the functioning of the dACC. High TSPO in brain regions that subserve declarative memory did not associate with performance in declarative memory as measured by tests of verbal memory or pattern separation/completion. While these findings suggest that the neuroimmune response in declarative memory circuits may not be related to declarative memory performance in VS-PWH, we acknowledge that our battery did not include other standard list learning and retrieval tests (e.g., Hopkins Verbal Learning Test-Revised). It is possible that those other metrics of declarative memory performance may prove to relate to TSPO levels in declarative memory circuits.

An association was found in VS-PWH between greater self-reported cognitive symptom burden (Factor 1) and higher TSPO in each of the cognitive control regions and in the PFC. That factor score of self-reported cognitive symptom burden consisted of four measures of self-reported cognitive control and one measure of self-reported declarative memory (Table 3). Since cognitive control, by definition, affects performance in other cognitive domains, it is reasonable to infer that a heightened immune response in cognitive control regions may have effect on the subjective experience in broader cognitive performance across domains.

Future work in VS-PWH would benefit from adding more self-report measures of memory and functioning across cognitive constructs to test further whether a broad, self-reported cognitive symptom burden associates with higher TSPO in cognitive control regions.

We acknowledge this was a relatively well-treated population of VS-PWH that performed at the level of the controls in cognitive control and declarative memory assessments. Future studies are needed to examine more impaired VS-PWH, other RDoC systems, and the hypothesized role of the neuroimmune response on longitudinal cognitive changes in VS-PWH. While those additional lines of research are needed, these findings support the presence of a clinically-relevant neuroimmune response in VS-PWH, which may guide the design of clinical trials using emerging, TSPO-targeting therapies.[44]

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 would 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, Michael Merickel, Allen Best, and Jared Sanderfeld (software engineering and design). The authors gratefully acknowledge the contributions of the study participants and staff at these two MWCCS sites as well as the study participants and staff of the Johns Hopkins Clinical Outcomes Core Cohort.

Funding:

This work was supported by the National Institutes of Health (MH119947 [Rubin, Maki], MH075673 [Rubin, Clements, Slusher]) and by the MWCCS Baltimore (U01-HL146201, Todd Brown and Joseph Margolick) and Metropolitan Washington (U01-HL146205, Seble Kassaye and Daniel Marenstein) clinical research sites and the Data Analysis and Coordinating Center (U01-HL146193, Gypsyamber D'Souza, Stephen Gange, and Elizabeth Topper). The contents of this publication are solely the responsibility of the authors and do not represent the official views of the NIH.

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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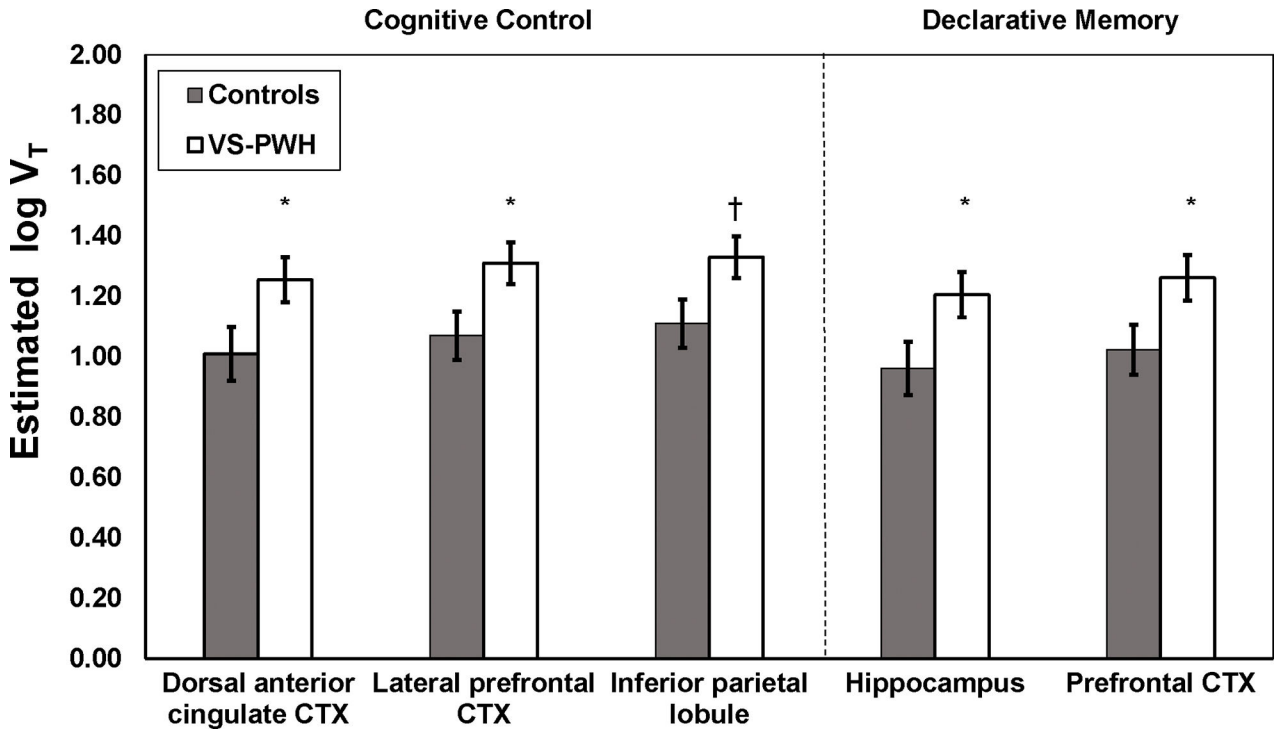

Figure 1. In rs6971 genotype-adjusted analyses, virally-suppressed people with HIV (VS-PWH) had higher log [^{11}C]DPA-713 V_T compared to HIV-uninfected individuals (Controls) in brain regions subserving cognitive control or declarative memory.

Mean log [^{11}C]DPA-713 V_T is shown for each region of interest subserving cognitive control or declarative memory. Error bars reflect standard error. CTX, Cortex. Significance of the group comparison in each region is marked *P<0.05 or †P=0.05.

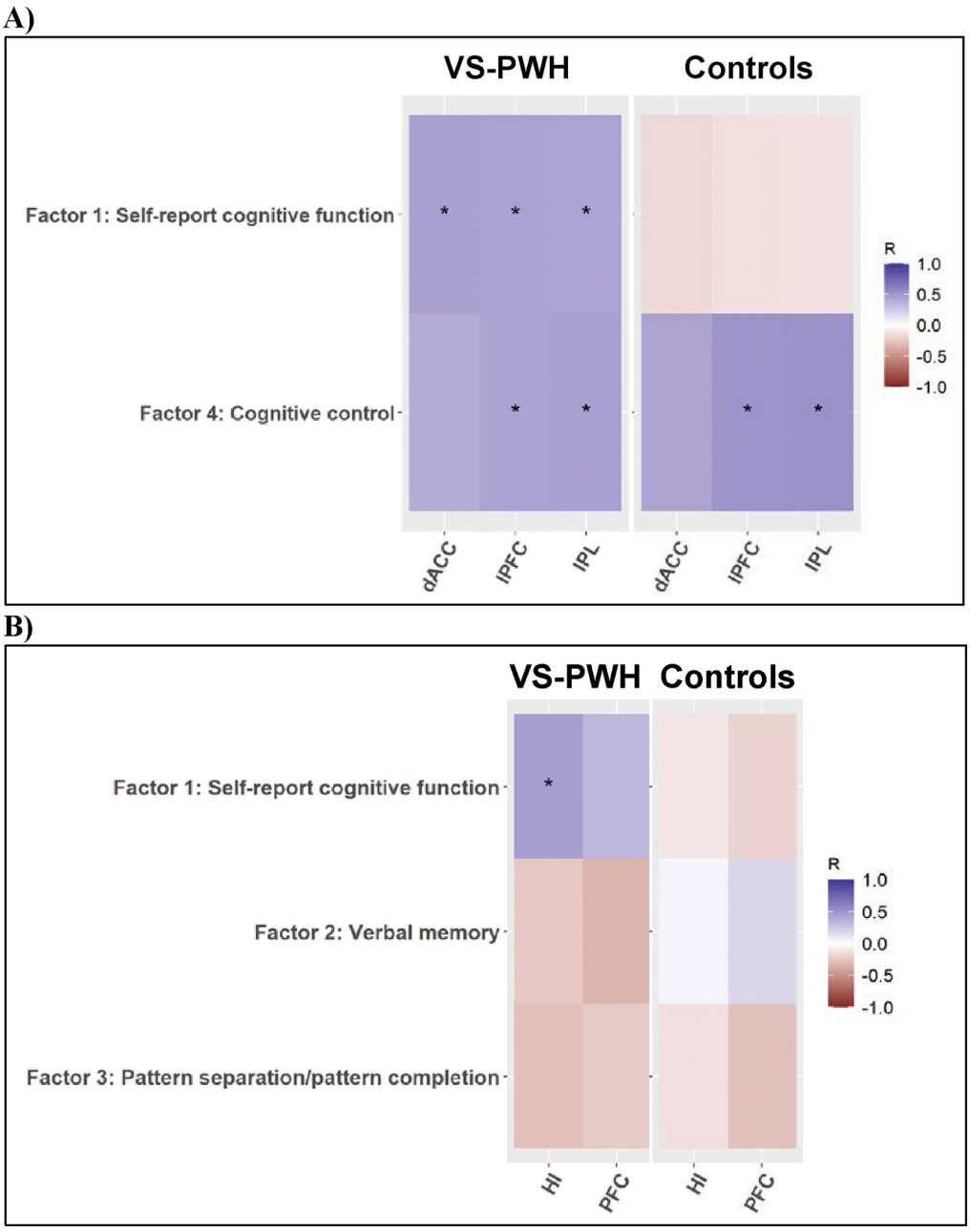

Figure 2. Partial correlations between log [^{11}C]DPA-713 V_T values in A) cognitive control or B) declarative memory regions of interest and relevant cognitive outcomes, adjusted for rs6971 genotype.

**P*<0.05 meeting false discovery rate correction. Controls=HIV-uninfected individuals; dACC=dorsal anterior cingulate; HI=hippocampus; lPFC=lateral prefrontal cortex; IPL=inferior parietal lobule; PFC=prefrontal cortex; VS-PWH=virally-suppressed people with HIV.

Table 1.

Subjective and objective metrics of cognitive performance using the Research Domain Criteria (RDoC) framework to assess cognitive control and declarative memory.

Cognitive system	Brain Regions	Subjective, Self-reported Metric	Objective Metric
Cognitive control	Lateral PFC, Inferior parietal lobule, dACC	BRIEF-shift, inhibit, and monitor subscales[28]; CFQ-distractibility subscale[30, 31], Barratt Impulsiveness Scale[29]	**Go/No-go** (RT cost between No-go and Go trials), **Eriksen Flanker Test**[39–41] (RT cost between incongruent and congruent trials)
Declarative memory	Hippocampus, Prefrontal Cortex	CFQ-forgetfulness subscale[30, 31]	**Buschke Selective Reminding Task**[22–25] (trial 1, learning slope, and words recalled on delayed free recall); **Behavioral Pattern Separation Task-Object version**[26, 27] (percentage of lures identified as “old” and “similar”)

CFQ=Cognitive Failures Questionnaire; dACC=dorsal anterior cingulate cortex; BRIEF= Behavior Rating Inventory of Executive Function-Adult Version; RT=reaction time

Table 2.

Characteristics of the virally-suppressed (VS)-PWH and HIV-uninfected individuals (Controls).

	VS-PWH (n=25)	Controls (n=18)	*P*-value[a]
Sociodemographics			
Age, M (SD)	56.60 (10.21)	58.89 (8.86)	0.45
Years of Education, M (SD)	14.20 (1.93)	14.67 (2.52)	0.55
WRAT-3 reading subtest, scaled score, M (SD)	102.13 (14.87)	108.73 (9.95)	0.14
Male, n (%)	16 (64)	12 (67)	0.86
Race, n (%)			0.35
Black	15 (60)	8 (44)	
White	10 (40)	9 (50)	
Asian	0 (0)	1 (6)	
TSPO Genotype, high-affinity binder	16 (64)	9 (50)	0.36
Mental health			
PHQ-9 total score, M (SD)[b]	3.68 (4.84)	2.72 (3.59)	0.48
GAD-7 total score, M (SD)[b]	2.44 (3.07)	2.22 (3.52)	0.83
Any sexual/physical childhood trauma, n (%)	8 (33)	7 (39)	0.71
Substance Use			
Marijuana use in past month[T]	6 (24)	4 (22)	0.89
CAT-MH alcohol use in past month			0.11
0 days	11 (44)	7 (39)	
1–10 days	10 (40)	9 (50)	
11–20 days	4 (16)	0 (0)	
21–30 days	0 (0)	2 (11)	
Most common ART drugs, n (%)			
Emtricitabine	16 (64)		
Tenofovir alafenamide	14 (56)		
Bictegravir	11 (44)		
[^{11}C]DPA-713 at time of injection			
Molar Activity (GBq/μmol), M (SD)	300.62 (94.46)	284.18 (79.84)	0.55
Injected dose of radioactivity (MBq), M (SD)	697.73 (15.52)	701.87 (14.23)	0.38
Injected mass (μg), M (SD)	0.96 (0.46)	0.99 (0.34)	0.85
***CC and DM Factor scores*, M (SD)**			
Factor 1: Self-reported cognitive symptom burden[b]	0.03 (1.04)	−0.04 (0.96)	0.83
Factor 2: Verbal memory[c]	−0.12 (1.02)	0.16 (0.98)	0.38
Factor 3: Pattern separation and completion[d]	−0.13 (0.96)	0.18 (1.05)	0.32
Factor 4: Cognitive control[b]	0.10 (0.93)	−0.13 (1.09)	0.46

ART=antiretroviral; CC=cognitive control; DM=declarative memory; VS-PWH=virally suppressed people with HIV; M=mean; SD=standard deviation; WRAT=Wide Range Achievement Test

[T] based on urinary toxicology

[a] *P*-values from comparison using student's t test or chi-square test as appropriate.

[b] higher scores=more behavioral problem/symptom burden

[c] higher scores=better performance

[d] greater problems with pattern separation

Table 3.

Results of the principal components factor analysis with varimax rotation in the total sample using the cognitive control and declarative memory self-report and behavioral metrics.

	Factor loadings			
	1	**2**	**3**	**4**
Factor 1: Self-reported cognitive function				
CFQ Distractibility subscale score	**0.88**	−0.09	0.08	0.14
CFQ Forgetfulness subscale score	**0.87**	−0.02	0.07	0.10
BRIEF inhibit subscale score	**0.86**	0.16	−0.35	0.07
BRIEF Shift subscale score	**0.73**	−0.12	0.00	−0.17
BRIEF Monitor subscale score	**0.65**	−0.25	−0.13	0.16
Factor 2: Verbal memory				
BSRT delayed recall	−0.15	**0.86**	0.07	−0.03
BSRT trial 1	−0.14	**0.74**	−0.10	0.21
BSRT learning slope	0.19	**0.68**	0.05	−0.39
Factor 3: Pattern separation and completion				
BPS-O percent identified as “similar” lures	0.13	0.03	**0.84**	0.11
BPS-O percent identified as “old” lures	0.12	0.05	**−0.83**	0.06
Factor 4: Cognitive control				
Flanker RT cost: incongruent – congruent trials	0.17	0.08	0.01	**0.77**
Go/No-go RT cost: No-go – go trials	−0.28	−0.07	0.31	**0.53**
BIS total score	0.42	−0.19	−0.17	**0.53**
% variance explained	**29.3**	**14.7**	**14.3**	**11.2**

Barratt Impulsiveness Scale total score; BRIEF=Behavior Rating Inventory of Executive Function; BPS-O=Behavioral Pattern Separation Task-Object; BSRT=Buschke Selective Reminding Test; CFQ=Cognitive Failures Questionnaire; RT=reaction time