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Microglial activation is inversely associated with cognition in individuals living with HIV on effective antiretroviral therapy

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Abstract

Objective: Despite viral suppression, HIV-associated cognitive impairment persists and may be partially due to persistent immune signalling by cells of the myeloid-lineage. Here, we aimed to understand the contribution of activated microglia located in vulnerable brain regions (e.g. frontal, subcortical) of HIV-infected, virally suppressed (HIV+VS) individuals in relation to cognitive and motor function.

Design: Twenty-one HIV+VS individuals underwent PET with [^{11}C]DPA-713 to image the translocator protein 18kDa (TSPO), a marker of microglial activation, and completed a comprehensive neuropsychological test battery.

Methods: Multivariable linear regressions were used to examine the contribution of [^{11}C]DPA-713 binding to cognitive performance.

Results: Higher [^{11}C]DPA-713 binding was associated with lower cognition among HIV+VS individuals. [^{11}C]DPA-713 binding in middle frontal gyrus/frontal cortex, hippocampus/temporal cortex and occipital cortex was inversely associated with performance on a number of cognitive domains, including verbal memory, processing speed/attention/concentration, executive function, working memory and motor function. [^{11}C]DPA-713 binding in parietal cortex, cerebellum and thalamus was associated with only specific cognitive domains including visual construction and verbal memory. Binding was not associated with global cognitive performance.

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Conflicts of interest

None.

Conclusion: The findings add to the growing body of evidence that immune-mediated brain injury may contribute to domain specific, HIV-associated, cognitive vulnerabilities despite viral suppression.

Keywords

cognition; HIV; neuroinflammation

Introduction

Milder forms of cognitive impairment persist among HIV-infected individuals including those on effective antiretrovirals [1–4]. In our longitudinal work in the Women's Interagency HIV Study, HIV-infected virally suppressed (HIV+VS) women showed global cognitive impairment versus HIV-uninfected (HIV−) women [1]. Global cognitive impairment was driven by vulnerabilities in learning and memory, attention, executive function, working memory, fluency and motor skill [1]. Given that HIV does not affect all cognitive domains equally, focusing on the mechanisms contributing to domain-specific vulnerabilities rather than just global impairment may help to advance our understanding of key mechanistic pathways as well as facilitating treatment advancement.

The fact that cognitive impairment remains prevalent in HIV+VS individuals demonstrates a need to look for mechanistic cause extending beyond the direct effects of the virus on the brain. It is clear that HIV itself and both Tat and gp120 directly alter the brain [5–10]. Although antiretrovirals prevent viral replication, immune reconstitution is often incomplete leading to chronic inflammation and low $CD4^+$ cell counts [11]. Even when antiretrovirals restore $CD4^+$ cell counts, chronic inflammation remains and is strongly predictive of multiple HIV-related comorbidities including cognitive impairment. This sustained, systemic inflammation has been shown to be the consequence of HIV-mediated destruction of the gut mucosa, and of intracellular HIV DNA in tissues, lymph nodes, circulating cells (e.g. monocytes) and the brain [12,13]. There is evidence that HIV-associated brain injury stems indirectly from immunological processes, particularly neuroinflammatory pathways mediated by cells of the monocyte/macrophage lineage [14–21]. Activated HIV-infected monocytes migrate across the blood-brain barrier, infecting microglia and macrophages, which in turn lead to an overexpression of cytokines and chemokines and the initiation of an astrocyte-induced inflammatory cascade [22–25]. Persistent monocyte-related activation as indexed by levels of soluble markers (CD163, CD14) shed by monocytes/macrophages [26,27] and markers of microglial activation *in vivo* [28–31] are associated with cognitive vulnerabilities among HIV+VS individuals. Findings underscore the importance of examining neuroinflammation as a key mechanism contributing to cognitive impairment in HIV+VS individuals.

As chronic neuroinflammation is a central candidate mechanism contributing to cognitive impairment in HIV+VS individuals, we now focus on chronic neuroinflammation in relation to domain-related vulnerabilities rather than global cognitive impairment. We used [^{11}C]DPA-713 with PET to image the translocator protein 18 kDa (TSPO), which is normally expressed at low levels in brain tissue and is greatly increased in expression by

activated microglia, as well as reactive astrocytes [32,33]. TSPO is a proposed biomarker for brain injury and repair that can now be measured in living individuals using radiotracers and PET imaging [34,35]. We have characterized the use of [^{11}C]DPA-713 with PET to image the distribution of TSPO in health and disease [29,36]. Using [^{11}C]DPA-713 PET, we previously demonstrated higher binding in the cingulate and white matter in HIV+VS versus HIV-VS individuals [29]. Here, we extend our previous work to investigate the relationship between regional [^{11}C]DPA-713 binding in the brains of HIV+VS individuals and performance on a comprehensive battery of standard neuropsychological tests.

Methods

Participants included 21 HIV+VS (17 men; 16 Black, non-Hispanic) individuals (plasma HIV RNA <50 copcopies/ml; 100% on antiretrovirals) chronically living with HIV [median 14 years; interquartile range (IQR) = 10] from Coughlin *et al.* [29] who completed neuropsychological testing. Participants were between 27 and 59 years of age [mean = 47.7, standard deviation (SD) = 8.2] and had between 10 and 16 years of education (mean = 12.8, SD = 1.6). The median nadir CD4$^+$ cell count was 200 (IQR = 273). Ninety percent of the sample were on nucleoside reverse transcriptase inhibitors, 67% on protease inhibitors, 48% on nonnucleoside reverse transcriptase inhibitors, 10% on integrase inhibitors and 5% on a C-C chemokine receptor type 5 (CCR5) receptor antagonist. All participants were from the Baltimore area and were not actively using alcohol or illicit substances or over-the-counter anti-inflammatory medications; however, eight participants were current and 15 were former smokers. Participants had no history of a head injury or surgery in the past year.

Neuropsychological tests included Digit Symbol Substitution Test (DSST) [37] or Symbol Digit Modalities Test (SDMT) [38] measures processing speed (total correct); Trail Making Test (TMT) [39] measures attention/concentration (Part A) and mental flexibility (Part B) (time to complete); Odd Man Out [40,41] measures executive function (total correct); Letter-Number Sequencing [37] measures working memory (total correct); Controlled Oral Word Association Test [42] measures verbal fluency (total correct words generated); Grooved Pegboard [43] measures fine motor skills (average time to complete dominant and nondominant hands); *Rey–Osterrieth* complex figure *test* (ROCF) [44] measures visual construction and memory (total correct); and Rey Auditory Verbal Learning Test (RAVLT) [44] or Hopkins Verbal Learning Test (HVLT) [45] measures of learning and memory (total words generated across learning trials and during delayed free recall, total correct words identified during recognition minus false positives). Given that participants either completed DSST or SDMT, scores were transformed into within-sample *z*-scores to yield a single measure. The same procedure was applied to the RAVLT/HVLT. Timed measures were multiplied by −1 so higher values equate to better performance. A global measure of cognition was also computed (total sum of standard deviation points based on the *z*-score for each outcome). According to the Frascati criteria [46], seven participants were cognitively normal, one had asymptomatic neurocognitive impairment, five had mild neurocognitive disorder and eight had HIV-associated dementia.

Image generation, processing and calculation of outcome measures

In brief, participants completed a 90-min PET assessment [29]. [^{11}C]DPA-713 was synthesized as previously described [47]. PET images were acquired using a CPS/CTI High Resolution Research Tomograph (CPS Innovations, Inc., Knoxville, Tennessee, USA), which has an axial spatial resolution (full width at half maximum) of 2.4 mm and an in-plane resolution of nearly 2.4 mm [48]. Arterial blood samples were collected over the dynamic PET emission scan to determine radioactivity in plasma. The 90-min listmode PET data, binned into 30 frames, were reconstructed using the iterative ordered subset expectation maximization algorithm [49]. PET data were analysed with PMOD, version 3.7 (PMOD Technologies, Zurich, Switzerland). [^{11}C]DPA-713 total distribution volume, defined as binding of the radiotracer in tissue relative to that in blood at equilibrium [50], was estimated using Logan analysis with a metabolite-corrected arterial input function. The primary binding outcome was regional [^{11}C]DPA-713 total distribution volume relative to [^{11}C]DPA-713 total distribution volume in gray matter, herein referred to as [^{11}C]DPA-713 total distribution volume ratio. Regions of interest (ROIs) were segmented from each structural MRI [29], and included cortical (frontal, parietal, occipital, temporal, cingulate) and subcortical (hippocampus, thalamus) regions. The middle frontal gyrus (MFG) within the frontal cortex was also defined given its importance in previous HIV neuroimaging studies [51–55].

Statistical analysis

Stepwise linear regressions were conducted in SAS, version 9.4 (SAS Institute Inc., Cary, North Carolina, USA) to determine the linear combination of regional [^{11}C]DPA-713 binding estimates associating with cognition. Given the influence of the rs6971 polymorphism in TSPO on the affinity of [^{11}C]DPA-713 for the TSPO target, *TSPO* (rs6971) genotype (C/C–high affinity binding phenotype, $n = 13$; C/T–mixed affinity binding phenotype, $n = 8$) was included as a covariate. Significance was set at a P value less than 0.05; trends P value more than 0.05 and P value less than 0.10.

Results

Among HIV+VS individuals, for many regions, there were associations between [^{11}C]DPA-713 binding and cognitive performance (Table 1). In general, [^{11}C]DPA-713 binding was inversely associated with cognitive performance. Higher binding in the MFG/frontal cortex was associated with lower verbal memory, executive function, working memory and motor function (Fig. 1a—d). In addition, higher binding in the cerebellum or temporal cortex, and lower binding in the thalamus were associated with lower verbal memory. Higher binding in the hippocampus was associated with lower executive and motor function, whereas higher binding in the parietal cortex was associated with lower visual construction. Higher binding in the occipital cortex was associated with lower working memory. Regional binding was not associated with verbal fluency, verbal learning, visual memory or global cognitive function.

Complementing our analyses within each defined ROI, mean parametric images of [^{11}C]DPA-713 V_T ratio were generated using Logan analysis and the PET data from the population of HIV+VS individuals. These images visually demonstrate the high V_T ratios across cortical and subcortical areas within individuals of each genotype (Fig. 1e).

Discussion

These data from combining in-vivo [^{11}C]DPA-713 PET and a comprehensive standard battery of neuropsychological tests are consistent with a detrimental link between higher microglial activation and lower domain-specific cognitive function among effectively treated HIV-infected individuals. Of the regions examined, binding in MFG/frontal cortex, temporal cortex/ hippocampus and occipital cortex was linked to lower performance across a number of domains, including verbal memory, processing speed/attention/concentration, executive function, working memory and motor function. Higher binding in the thalamus or lower binding in cerebellum was associated with better verbal memory. Binding in parietal cortex was related to lower visual construction. Together, these findings add to the growing body of evidence that immune-mediated central nervous system injury is an important contributor to HIV-associated cognitive vulnerabilities despite optimal treatment [28–30]. Moreover, these findings also suggest that microglial activation in the context of HIV may be important to some but not all cognitive domains.

In addition to large cortical and subcortical regions, we also assessed [^{11}C]DPA-713 PET binding in the targeted frontal subregion of the MFG, which makes up a large part of the human dorsolateral prefrontal cortex (DLPFC) [56,57]. Aberrant prefrontal activity during working memory performance has been demonstrated in HIV-positive women [52]. Previous functional MRI also supports HIV-related alterations in hippocampus-prefrontal activation during verbal and visual memory performance [55,58]. These findings suggest a link between microglial activation due to HIV and altered neuronal signalling in hippocampus-prefrontal pathways that contributes to domain-specific cognitive deficits and can be tested in future multimodal (PET, functional MR) imaging studies of HIV+VS individuals. The mechanistic links between disease, microglial activation and domain-specific cognitive performance may be probed with direct study of brain tissue using mouse models as done in psychosis [59], wherein the TSPO signal in medial prefrontal cortex of rodents is akin to the DLPFC in humans [60,61].

Although the directionality of our findings is consistent with the two previously conducted TSPO imaging studies among HIV+VS individuals [28,30], there are inconsistencies across studies regarding the pattern of associations between radiotracer binding and domain-specific cognitive performance. Among seven cognitively intact white HIV+VS men who completed the CogState computerized battery and [^{11}C]-PK11195 PET, higher radiotracer binding in cingulate cortex was associated with lower executive function [28]. A subsequent study used a second-generation radiotracer for TSPO with PET, as in our study, and reported that radiotracer binding estimates in several brain regions (hippocampus, amygdala, thalamus) were associated with lower global performance assessed using CogState [30] among 12 HIV+VS individuals. Associations were driven by performance on learning, memory and speed but not executive function. Although HIV+VS individuals had higher

radiotracer binding in occipital cortex versus controls, radiotracer binding in occipital cortex was associated with lower visual learning, whereas we found it to be inversely associated with both processing speed and working memory. Inconsistencies across studies could be due to differences in the cognitive assessment, sample size, radiotracer, segmented brain regions or participants' clinical characteristics (cognition, sociodemographic).

This is the largest study to date to examine the relationship between cerebral distribution of TSPO and cognition using PET in a mixed sample of cognitively intact and impaired HIV +VS individuals. Rather than examining the relationship between radiotracer binding and performance in each brain region separately, we utilized regressions to assess which brain regions demonstrate a notable association between radiotracer binding and domain-specific performance. This approach aligns with the networked nature of regional cerebral circuits underlying cognition. Although our study was limited by cross-sectional design, sample selection (convenience sample), lack of a control group and single cognitive tests within some domains, our results highlight imaging TSPO as a promising approach to understand the role of neuroimmunity in domain-specific cognition in HIV+VS individuals. Future longitudinal studies and prediction models using TSPO imaging with other immune markers in parallel, as well as complementary models probing microglia directly (e.g. postmortem and animal studies) are warranted in the setting of recognized complexity of both neuroimmunity and the functional roles of TSPO [62]. Moreover, future, larger studies examining the impact of sociodemographic (e.g. age, sex, race), behavioural and clinical factors are needed to further our understanding of the neuroimmune response in HIV-associated, domain-specific, cognitive decline.

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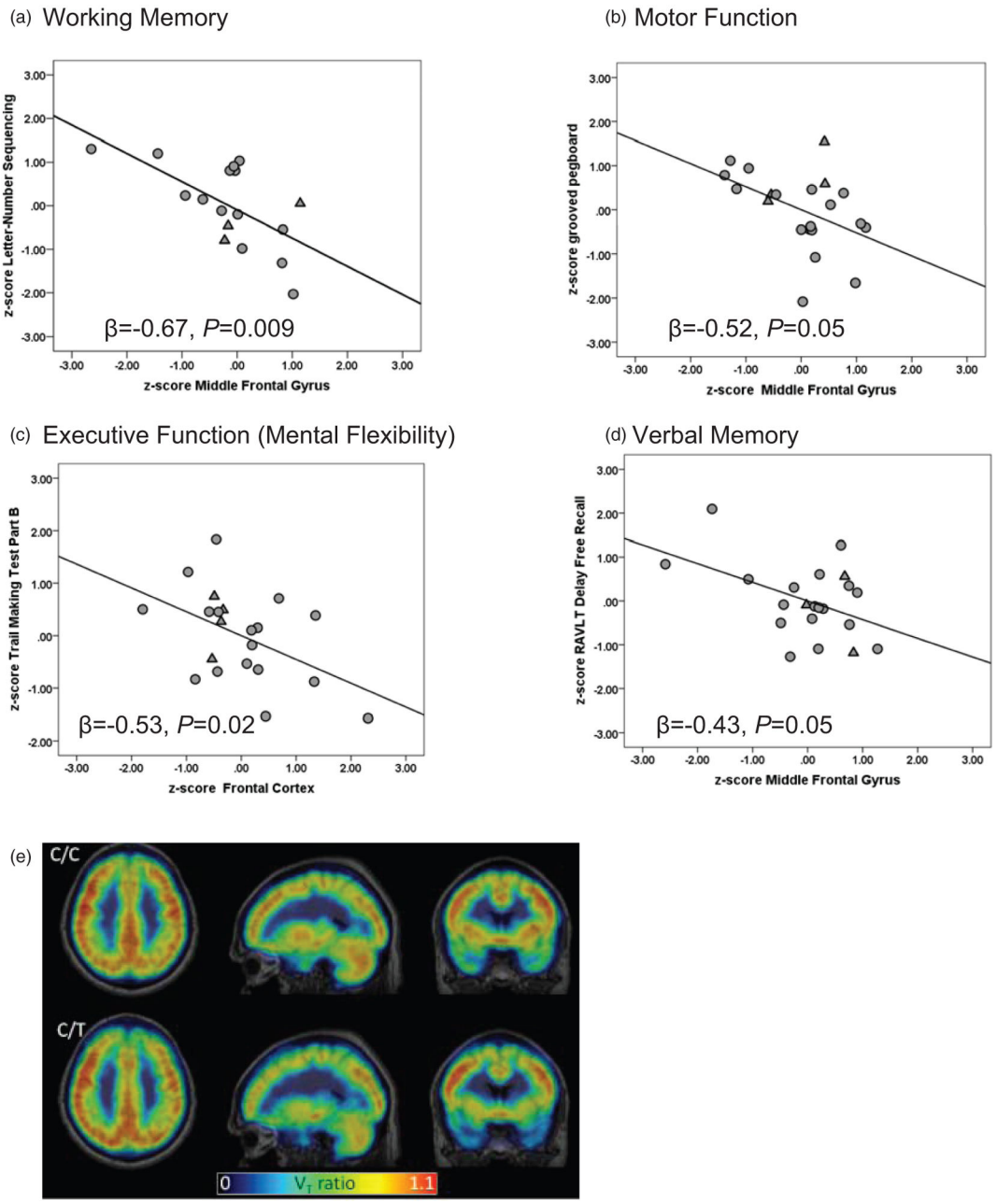

Fig. 1. Use of [^{11}C]DPA-713 PET in 21 HIV-infected virally suppressed (HIV+VS) individuals reveals an association between region-specific binding to TSPO and deficits in cognitive performance.

(a–d) Partial regression plots demonstrate associations between [^{11}C]DPA-713 VT normalized to VT in gray matter (VT ratio) in the frontal cortex or the middle frontal gyrus within frontal cortex and cognitive function in HIV+VS individuals. (e) Mean parametric images of [^{11}C]DPA-713 VT ratio, displayed in three views (left to right: axial, sagittal, coronal) from HIV+VS individuals of C/C (n = 13) or C/T (n = 8) TSPO genotype. VT is in units of mL/cm^3 and VT ratio is unitless. Circles, men; Triangles, women. RAVLT, Rey Auditory Verbal Learning Test.

Table 1.

Regional [^{11}C]DPA-713 V_T ratio was associated with cognitive performance among 21 HIV-infected virally suppressed individuals.

	Model statistics				
Final models	**β**	**SE**	***P***	**R^2 Δ**	**Total R^2**
Learning					
RAVLT/HVLT learning across trials	–	–	–	–	–
Verbal/Visual memory					
RAVLT/HVLT delay free recall					
Thalamus	0.48	0.26	***0.08***	0.05	
Cerebellum	−0.57	0.22	**0.02**	0.12	
Middle frontal gyrus	−0.43	0.21	***0.05***	0.14	0.31
RAVLT/HVLT recognition					
Temporal cortex	−0.80	0.21	**0.001**	0.11	
Middle frontal gyrus	−0.57	0.18	**0.006**	0.27	
Thalamus	0.48	0.23	**0.04**	0.11	0.49
Rey–Osterrieth delay free recall	–	–	–	–	–
Processing speed, Attention/Concentration					
Digit Symbols					
Occipital cortex	−0.54	0.21	**0.02**	0.19	0.19
Trail Making Test Part A					
Hippocampus	−0.44	0.24	***0.07***	0.08	0.08
Executive function					
Trail Making Test Part B					
Frontal cortex	−0.53	0.19	**0.02**	0.18	
Hippocampus	−0.45	0.20	**0.04**	0.15	0.33
Odd Man Out Task					
Middle frontal gyrus	−0.63	0.33	***0.05***	0.19	0.19
Working memory					
Letter-Number Sequencing					
Occipital cortex	−0.59	0.21	**0.02**	0.08	
Middle frontal gyrus	−0.67	0.22	**0.009**	0.27	0.35

	Model statistics				
Final models	**β**	**SE**	***P***	**R^2 Δ**	**Total R^2**
Visual construction					
Rey–Osterrieth figure copy					
Parietal cortex	−0.50	0.20	**0.04**	0.20	0.20
Verbal fluency					
Controlled Oral Word Association Test	–	–	–	–	–
Motor function					
Grooved pegboard					
Hippocampus	−0.84	0.27	**0.007**	0.13	
Middle frontal gyrus	−0.52	0.25	***0.05***	0.14	0.27
Global Function	–	–	–	–	–

Bolded *P* values are significant at $P < 0.05$; bolded and italicized are considered trends at $P < 0.10$. All models controlled for TSPO genotype. Δ, change; β, standardized beta weight; HVLT, Hopkins Verbal Learning Test; RAVLT, Rey Auditory Verbal Learning Test; SE, standard error.