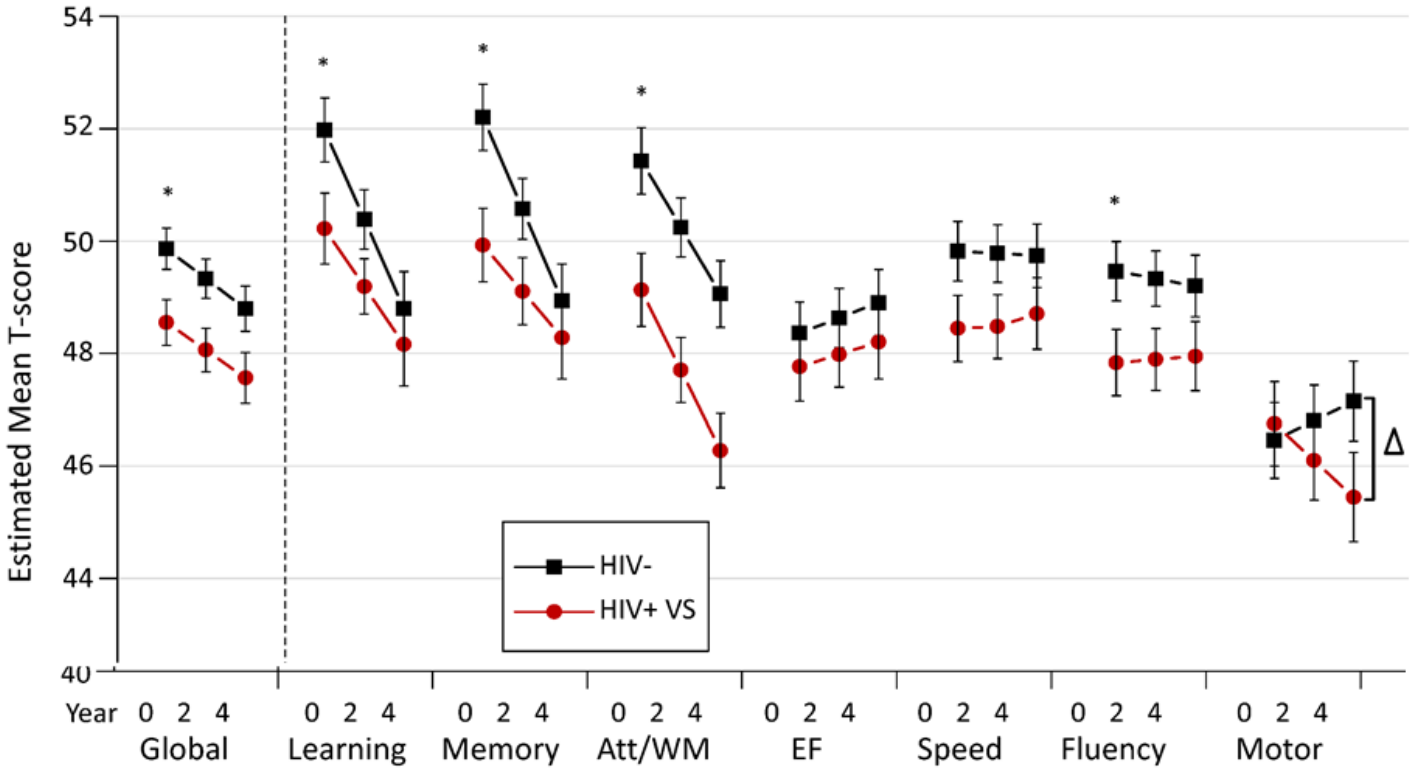
Assessing the contribution of glial activation to cognitive control and declarative memory in virally-suppressed people with HIV

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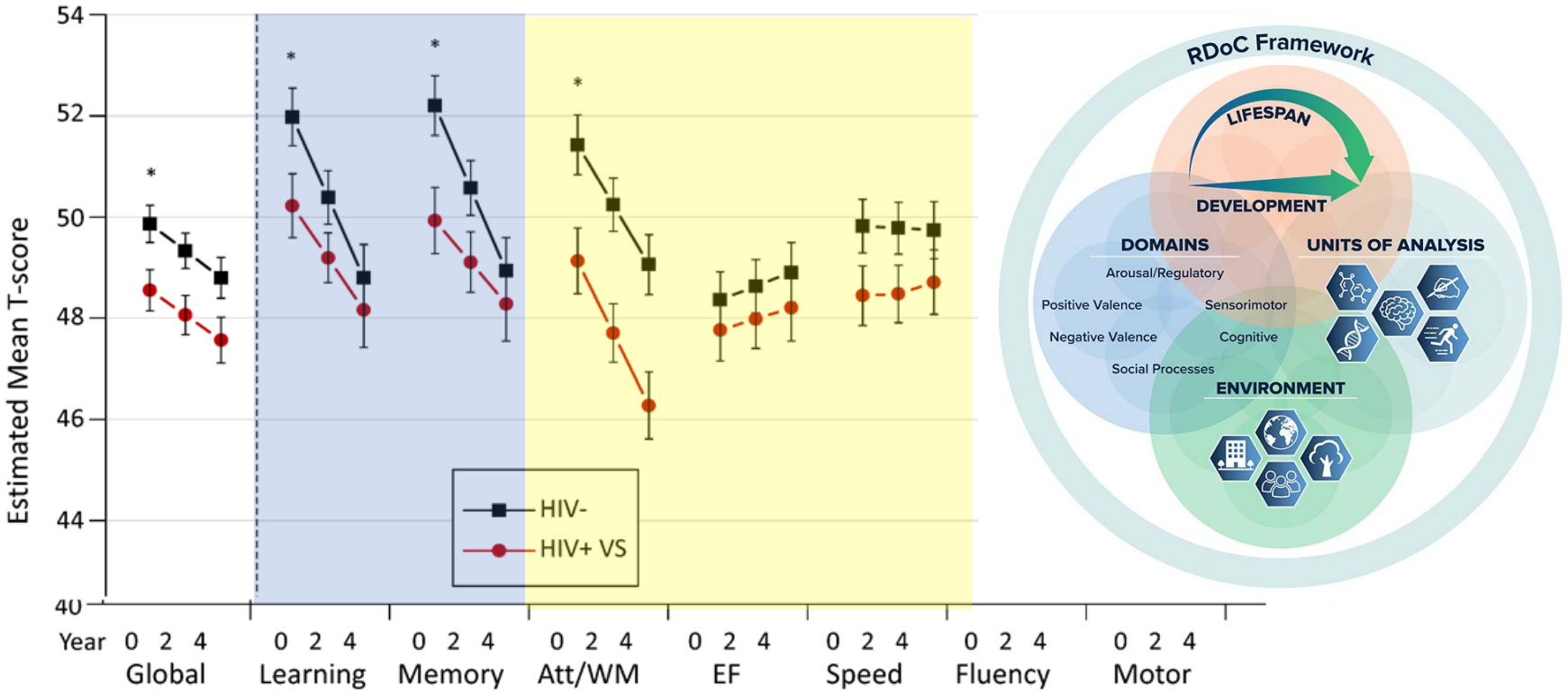
Cognitive complications persist among virally-suppressed people with HIV



Note. VS= refers to consistent use of cART and virally suppressed over the 4 year study duration; Att/WM=attention/working memory; EF=executive function; Δ=significant group difference in slopes at $p<0.05$.

Rubin et al. *Neurology* 2017

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Need to examine the mechanistic etiology

Microglia: the resident neuroimmune cells in the brain

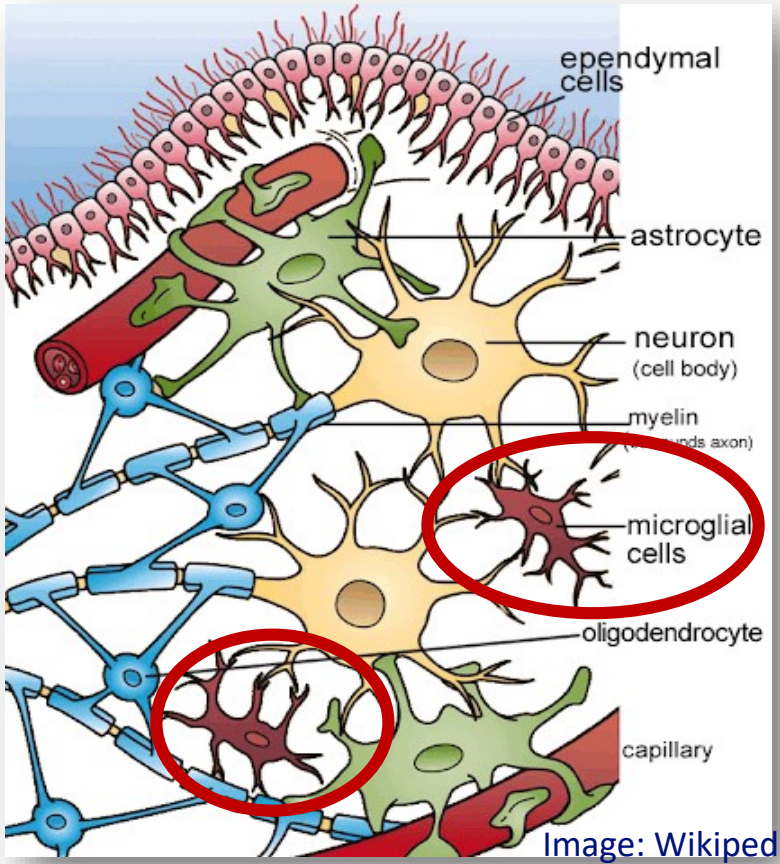
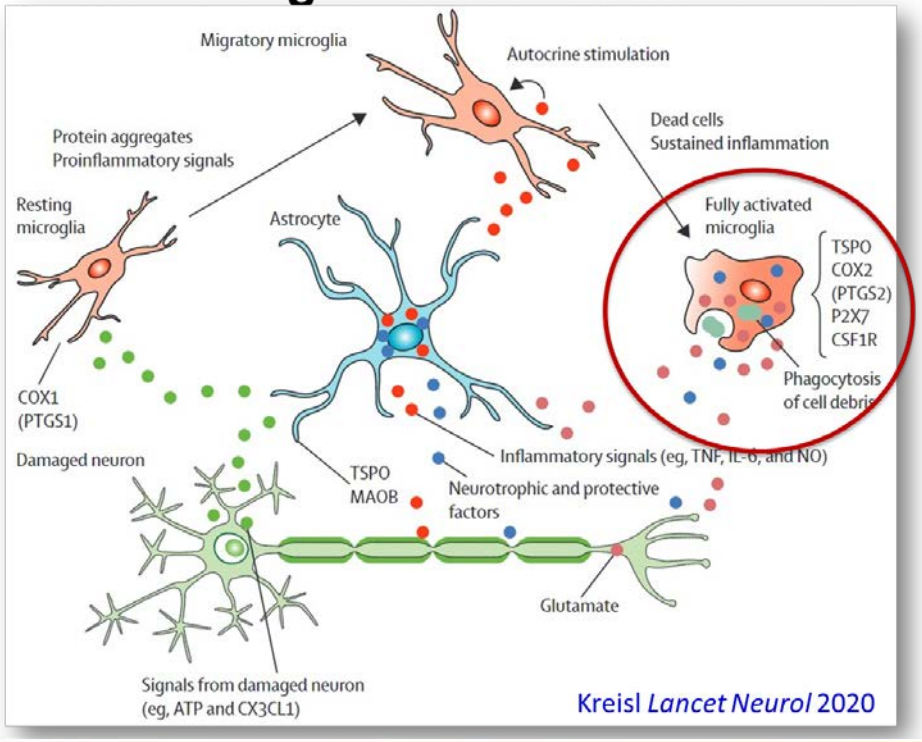


Image: Wikipedia

PET-based imaging to detect & localize the immune response



Immune targets in the brain for PET



Imaging targets for detecting inflammation

	Radioligand	Cell distribution	Function
TSPO	Several	Microglia; astrocytes; vascular endothelium	Unclear, possibly steroid synthesis
MAO-B	[^{11}C]SL25.1188	Astrocytes; serotonin-releasing neurons	Metabolism of non-serotonergic monoamines; hydrogen peroxide signaling
COX-1	[^{11}C]PS13	Microglia (primarily)	Prostanoid synthesis
COX-2	[^{11}C]MC1	Microglia; neurons	Prostanoid synthesis
CSF1R	[^{11}C]CPPC	Microglia (exclusively)	Regulation of mononuclear phagocytes
P2X7R	[^{11}C]JNJ-54173717 [^{18}F]JNJ-64413739 [^{11}C]SMW139	Microglia (primarily); oligodendrocytes; astrocytes	Inflammatory cytokine release

Meyer *Lancet Psychiatry* 2020

Previous TSPO PET imaging studies in PWH

	PWH n (age % male)	PWoH n (age % male)	% CI PWH	TSPO PET radiotracer	PWH > PWoH TSPO binding	TSPO binding – cognition links in PWH
Hammoud (2005)	10 (45yrs, 100)	5 (41yrs, 80)	50	[^{11}C]R-PK11195	thalamus, putamen, cerebellum, frontal & occipital GM	• thalamus, putamen, frontal, temporal, & occipital GM- HAD
Wiley (2006)	12 (49yrs, n/a)	5 (40yrs, n/a)	50	[^{11}C]R-PK11195	none	-
Garvey (2014)	7 (48, n/a) HIV RNA <50cp/ml	9 (31 yrs, n/a)	100	[^{11}C]R-PK11195	CC, anterior & posterior cingulate, temporal & frontal GM	• CC, anterior & posterior cingulate - executive function
Vera (2016)	12 (42yrs, 100) HIV RNA <50cp/ml	10 (41yrs, 100)	0	[^{11}C]PBR28	parietal, occipital, & globus pallidus	• hippocampus & thalamus –learning & memory • hippocampus, right amygdala & thalamus – global function
Boerwinkle (2021)	24 (57yrs, 75) HIV RNA <200cp/ml	13 (59yrs, 69)	29	[^{11}C]PBR28	none	• total cerebral GM, thalamus, caudal middle frontal, frontal, occipital, & parietal GM- executive function • parietal GM – global function
Coughlin (2014)*	23 (46yrs, 80) HIV RNA <50cp/ml	12 (40yrs, 68)	40	[^{11}C]DPA-713	temporal & frontal GM, cingulate, supramarginal GM, WM	• frontal GM- HAD vs. asymptomatic+mild impairment • cingulate, temporal & frontal GM, & WM- asymptomatic vs. PWoH
Rubin (2018)*	21 (48yrs, 81) HIV RNA <50cp/ml	-	38	[^{11}C]DPA-713	-	• MFG, thalamus, cerebellum, & temporal GM–memory • MFG & occipital GM – working memory • occipital GM, MFG, & hippocampus-psychomotor speed • frontal GM, MFG, & hippocampus-executive function

CI=cognitive impairment (impaired on ≥2 domains); GM=gray matter; CC=corpus callosum; MFG=middle frontal gyrus; WH=white matter; *same participant pool

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Aims and Hypotheses

Aim: Use [11C]DPA-713 PET to assess the contribution of chronic inflammation contributing to impairment in cognitive control (CC) & declarative memory (DM) in VS-PWH.

Hypotheses:

- **VS-PWH (vs. PWoH) would show higher TSPO in brain regions that subserve CC (lateral prefrontal cortex, dorsal anterior cingulate, inferior parietal lobule) & DM (prefrontal cortex, hippocampus), &**

- **higher TSPO levels in these regions of interest would relate to poorer CC & DM on self-report or behavioral measures.**

Methods

- Participants completed a 90-min DPA-PET scan with arterial blood sampling, structural brain MRI, & CC & DM measures.
- Regional [^{11}C]DPA-713 total distribution volume (V_T) values estimated via Logan graphical analysis with metabolite-corrected arterial input function.
- Linear mixed model with repeated measures used to compare regional V_T values between groups controlling for TSPO rs6971 genotype.
- Partial correlations between regions of interest & CC/DM metrics, controlling for TSPO genotype.

Participant Characteristics

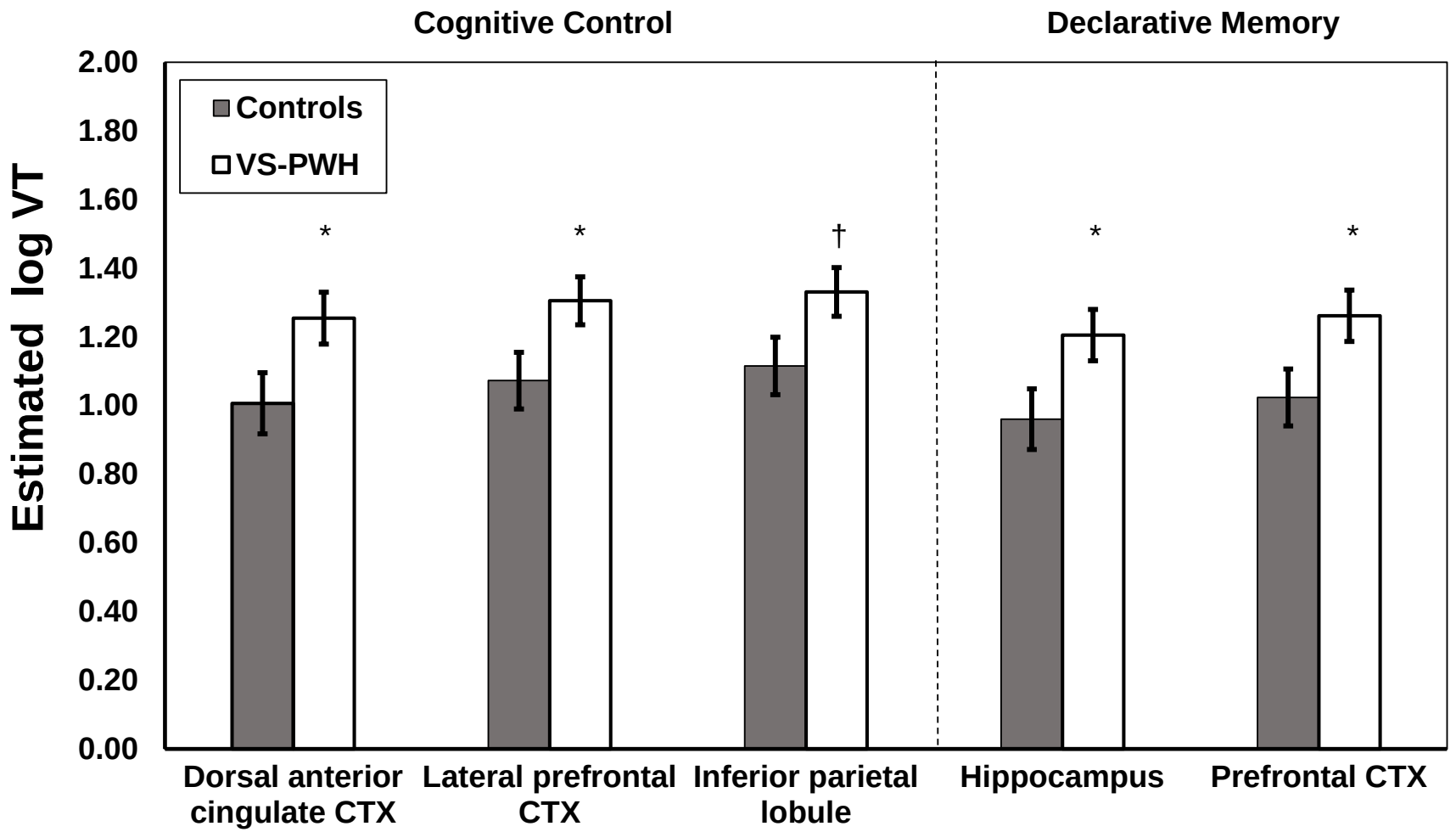
	VS-PWH (n=25)	PWoH (n=18)	*P*-value
Age, M (SD)	56.6 (10.2)	58.9 (8.9)	0.45
Years of education, M (SD)	14.2 (1.9)	14.7 (2.5)	0.55
Male, n (%)	16 (64)	12 (67)	0.86
Race, n (%) Black White Other	 15 (60) 10 (40) 0 (0)	 8 (44) 9 (50) 1 (6)	0.35
TSPO Genotype, CC	16 (64)	9 (50)	0.36
PHQ-9 total score, M (SD)	3.7 (4.8)	2.7 (3.6)	0.48
GAD-7 total score, M (SD)	2.4 (3.1)	2.2 (3.5)	0.83
Most common ART drugs, n (%) Emtricitabine TAF Bictegravir	 16 (64) 14 (56) 11 (44)		
[^{11}C]DPA-713 at time of injection			
Molar Activity (GBq/μmol), M (SD)	300.6 (94.5)	284.2 (79.8)	0.55
Injected dose of radioactivity (MBq), M (SD)	697.7 (15.5)	701.9 (14.2)	0.38
Injected mass (μg), M (SD)	0.96 (0.46)	0.99 (0.34)	0.85

NIMH RDoC battery assessing cognitive control (CC) & declarative memory (DM)

Subdomain/level		Circuits	Self-report	Paradigm (outcome)
Cognitive Control	Goal selection & updating	lateral PFC inferior parietal lobule dACC	BRIEF-shift subscale; CFQ-distractibility subscale	GNG (hits cost); Trail Making Test (Part B – Part A); NIH Toolbox Dimensional Card Sort Test
	Response selection, inhibition, suppression		Barratt Impulsiveness Scale; BRIEF-inhibit subscale	Stroop (RT cost), GNG (RT cost), Flanker Inhibitory Control & Attention Test
	Performance monitoring		BRIEF-monitor subscale	
Declarative Memory		Hippocampus, PFC	CFQ-forgetfulness subscale	Pattern Separation & Completion Test (similar and old lures); Buschke Selective Reminding Task (trial 1, learning across trials, and delayed free recall)

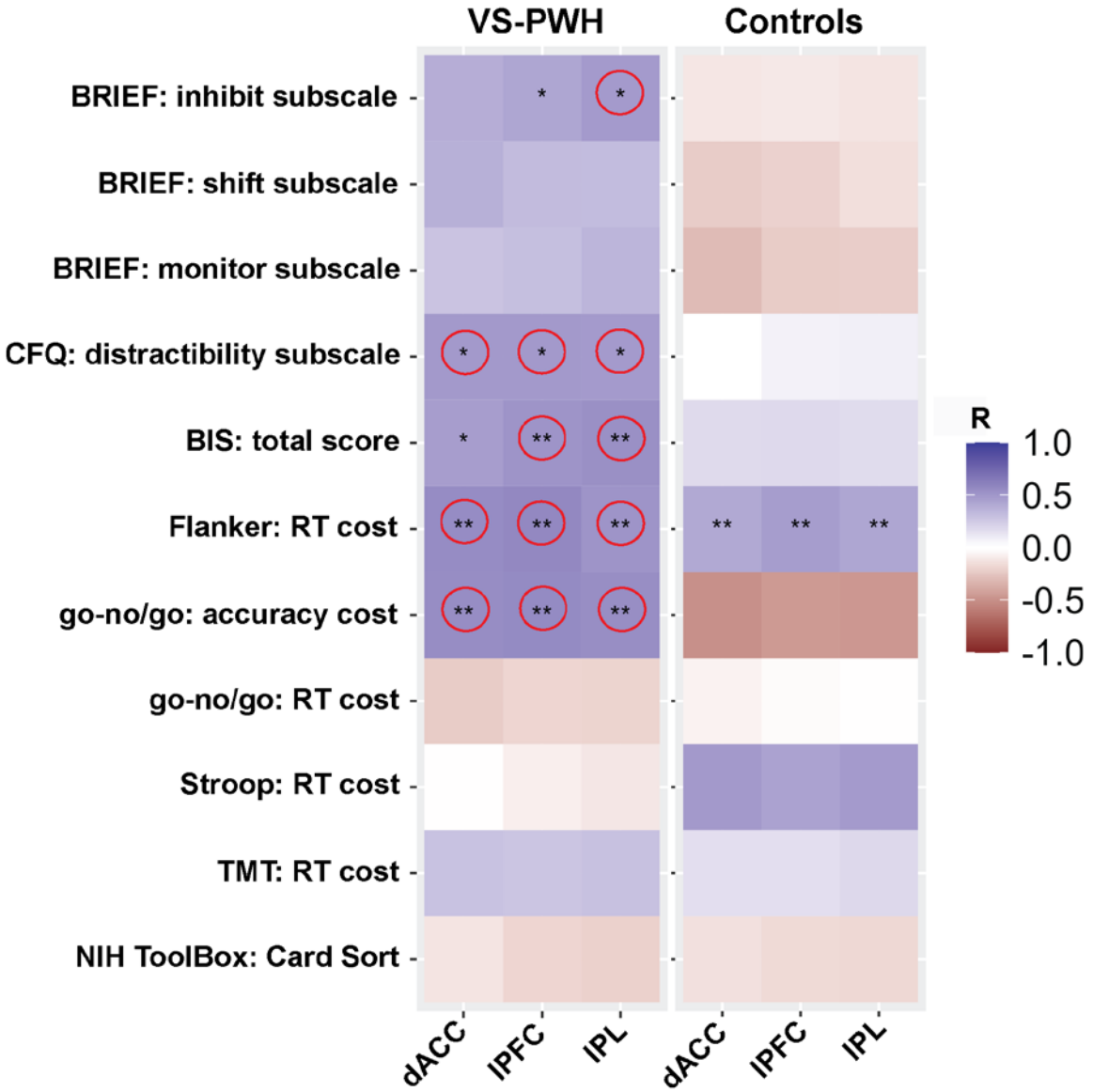
CFQ=Cognitive Failures Questionnaire; dACC=dorsal anterior cingulate cortex; BRIEF= Behavior Rating Inventory of Executive Function-Adult Version; GNG=go-no/go; PFC=prefrontal cortex; RT=reaction time

Higher TSPO in brain regions subserving cognitive control & declarative memory in VS-PWH vs. PWoH.



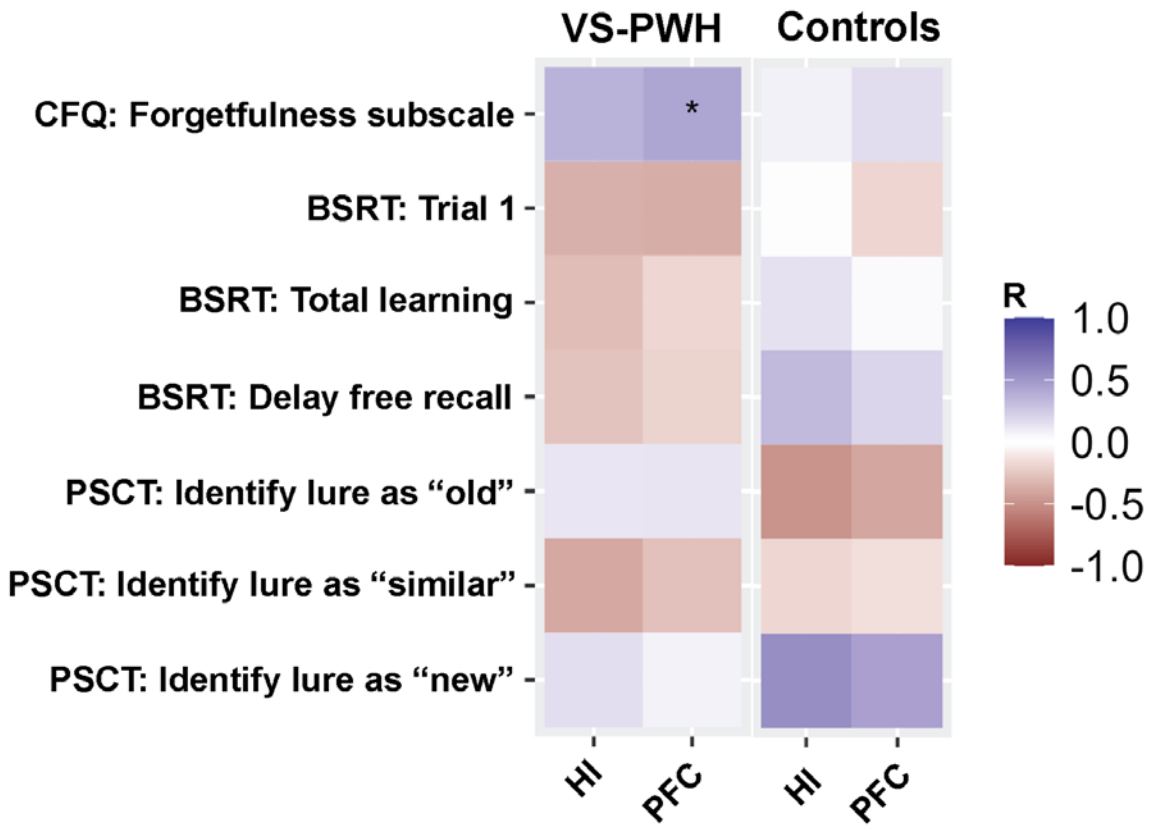
Estimated V_T is in units of mL cm^{-3} adjusted for TSPO rs6971 SNP genotype (C/C, C/T).
Error bars reflect standard error. CTX, Cortex. $^{*}P<0.05$; †$P=0.05$

TSPO in brain regions subserving cognitive control (CC) are related to CC performance metrics in VS-PWH and PWoH



***P<0.001; **P<0.01; *P<0.05
BIS=Barratt Impulsiveness Scale
BRIEF=Behavior Rating Inventory of Executive Function
CFQ=Cognitive Failures Questionnaire
dACC=dorsal anterior cingulate
lPFC=lateral prefrontal cortex
lPL=inferior parietal lobule
RT=reaction time
go-no/go was completed in the MRI scanner.
P-values are from partial correlations controlling for TSPO genotype

TSPO in brain regions subserving declarative memory (DM) are NOT related to DM performance metrics



****P*<0.05**
BSRT=Buschke Selective Reminding Task
CFQ=Cognitive Failures Questionnaire
HI=hippocampus
PFC=prefrontal cortex
PSCT=Pattern Separation & Completion Task
***P*-values are from partial correlations controlling for TSPO genotype**

Summary and Conclusions

- Localized microglial activation marked by higher TSPO in the cognitive control (CC) network may contribute to lower CC in VS-PWH.

- Conversely, associations with declarative memory were not evident.

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