Supplemental Digital Content 1. Review of HIV Structural MRI studies

PubMed was searched (keyword/title/abstract) using the following keywords: Structural, MRI, volume, HIV; and separately Structural, MRI, morphometry, HIV.

Studies were immediately excluded if they were

- Written in a language other than English,
- Not a published peer-reviewed original research article (e.g., review, commentary or conference abstracts),
- It was not stated that a majority of HIV+ individuals had received cART and had chronic HIV infection,
- Randomized clinical trials concentrating on comparing one cart regimen to another,
- Not studies in adults aged 18+

The selection process yielded 32 articles and 28 of which included neurocognitive testing.

The studies were then systematically reviewed in a non-blinded fashion.

Study	**Neurocognitive testing**	**How cognitive results were reported?**	**MRI & Neurocognition correlation**	**Was the HIV+ sample all virally suppressed?**	**MRI processing/ analytical platform**
1 Chao *et al.* 2003	Yes	Individual test scores	No	Yes	VBM
2 Castelo *et al.* 2007	Yes	Individual test scores	Putamen hypertrophy correlated with lower motor speed	No	ROI
3 Cohen *et al.* 2010	No (AIDS dementia complex staging scale used)	17% ADC stage ≥1 (mild, moderate or severe impairment) 83% Neuroasymptomatic	ADC stage was not a significant predictor of any of the brain volumes.	No	VBM
4 Becker *et al.* 2011 CVD substudy of MACS cohort	No	N/A	N/A	No	VBM DBM
5 Jernigan *et al.* 2011 CHARTER cohort	Yes	37% neurocognitively impaired (GDS≥0.5)	N/A	No	Some manual tracing ROI

6 Kuper *et al.* 2011	Yes	41.7% mild cognitive deficit (HIV Dementia Scale score (HDS) 14-11) 16.6% overt cognitive deficit (HDS ≤10) 41.7% No cognitive impairment (HDS ≥15)	Decreased GM volume in anterior cingulate and temporal cortices & reduced midbrain WM correlated with increasing cognitive decline Reduced basal ganglia correlated with greater motor dysfunction	No	VBM
7 Tate *et al.* 2011	Yes	83.8% No impairment + ANI (asymptomatic group) 16.2% MND +HAD (symptomatic group)	Greater cognitive impairment associated with smaller isthmus and genu	No	Manual tracing ROI
8 Ances *et al.* 2012	Yes	Individual test and composite neuropsychological summary Z-score (NPZ-4)	Poorer NP test scores in HIV+ but did not explore correlation with MRI outcomes	Yes	ROI
9 Becker *et al.* 2012 CVD substudy of MACS cohort	Yes	Individual test and NP summary scores	Greater atrophy in peri-ventricular white matter and frontal and temporal regions associated with poorer NP test performance Extensive regions of the anterior temporal lobe were linked to performance on the NP tests	No	VBM

10 Hua *et al.* 2013 HIV Neuroimaging Consortium cohort	Yes	61% ADC stage 0 25% ADC stage 0.5 (ANI) 12% ADC stage 1 (MND) 2% ADC stage 2 (HAD)	No	Yes	TBM
11 Kallianpur *et al.* 2013	No	N/A	N/A	Close to 100%	ROI
12 Archibald *et al.* 2014 CHARTER cohort	Yes	35% cognitively impaired as defined by HAND Fracati criteria	No	No	Partial manual tracing ROI
13 Keltner *et al.* 2014 CHARTER cohort	Yes	Mean GDS	No	No	Partial manual tracing ROI
14 Clark *et al.* 2015	No	N/A	N/A	No	ROI
15 Janssen *et al.* 2015	Yes	HIV+: 58.9 % NP normal 35.8% ANI 5.3% MND 0% HAD HIV-: 69.1% NP normal 30.9% ANI	Lower thalamic volume is related to a lower motor function performance in the patient group and lower speed of information processing in the controls	Yes	VBM

16 Ortega *et al.* 2015	Yes	NPZ scores	Motor function performance was associated with larger volumes of total gray matter total white matter and hippocampus	Yes	ROI
17 Wilson *et al.* 2015	Yes	52.9% scored in the impaired range on ≥ 2 domains of the neurocognitive battery	VBM metrics did not correlate with scores on any NP scores	Yes	VBM
18 Guha *et al.* 2016	Yes	Domain composite scores and global z score	HIV+ participants showed correlation between greater volumetric factor scores for the cortical topography and better global Z-scores and better psychomotor/processing speed Z-scores	No	ROI
19 Keltner *et al.* 2016 CHARTER cohort	Yes	Mean GDS	No	No	VBM
20 Rubin *et al.* 2016 WIHS consortium cohort	Yes	Domain z-scores	Smaller volume in the left hippocampus was associated with worse performance on the verbal memory composite Smaller inferior frontal gyrus (BA44) volume in the right hemisphere was significantly associated with worse performance on the verbal memory composite	No	ROI

21 Spies *et al.* 2016	Yes	Raw test scores	Significant associations between the left frontal lobe and speed of information processing, right ACC, motor skills and processing speed, left hippocampus, learning and language/verbal fluency, corpus callosum, language/verbal fluency, processing speed and attention/working memory, left amygdala, processing speed and abstraction/executive functioning, right amygdala and language/verbal fluency, left caudate, processing speed, abstraction/executive functioning and attention/working memory, respectively	No	ROI
22 Wendelken *et al.* 2016	Yes	47% NP normal 23% ANI 30% MND+HAD	No	No	TBM
23 Cole *et al.* 2017 Same COBRA cohort as Underwood el., 2017	Yes	19.1% per GDS ANI/MND/HAD not reported	Brain-Predicted Aging was inversely associated with cognitive performance	Yes	VBM
24 Sanford *et al.* 2017	Yes	Summary z-scores	Poorer NP test score correlated with larger lateral ventricles, cortical thickness reduction in left lateral temporal pole, left inferior occipital, right lateral occipital and right inferior lateral frontal cortices	Close to 100% (75%)	VBM, DBM, cortical modelling
25 Kuhn et al	Yes	Global and domain z-scores	Left hippocampal shape was positively associated with domains of	Close to 100% 54%	Shape analysis

2017			learning/memory, verbal fluency, executive functioning, and attention/processing speed. Right hippocampal shape was positively associated with domains of learning and memory, executive functioning, verbal fluency, and motor functioning. Right amygdala shape was only associated with verbal fluency, whereas left amygdala shape was positively associated with domains of attention/processing speed, verbal fluency, and motor functioning.		
26 Underwood *et al.* 2017 Same COBRA cohort as Cole et al. 2016	Yes	18% HIV+ and 3.8% HIV- cognitively impaired according to Frascati criteria 1.5% of HIV+ and 1.2% HIV- met criteria for HAD	Larger GM volume associated with better cognitive performance	Yes	VBM
27 Van Zoest *et al.* 2017 Same COBRA cohort as Cole et al. 2016 & Underwood et a., 2017	Yes	Not reported	Not reported	Yes	VBM
28 Clark *et al.* 2018	Yes	intra-individual variability on a reaction time measure	Greater RT-IIV associated with lower total WM and GM volume	Yes	ROI

29 Cole *et al.* 2018 Same COBRA cohort as Cole et al. 2016 & Underwood et a., 2017 & Van Zoest et al. 2017 + longitudinal data	Yes	Standardised domain T-scores and global T-score	PLWH had poorer global cognitive performance at baseline and were stable over time.	Yes	VBM ROI
30 Haynes *et al.* 2018	Yes	z-scores	No volume change over time and no association with NP scores	Yes	VBM
31 Sanford *et al.* 2018 Same cohort as Sanford et al 2017	Yes	Not reported	No	Yes	TBM, VBM, cortical modelling
32 Underwood *et al.* 2018 CHARTER cohort	Yes	37.4% Impaired (GDS ≥0.5) 4.3% HAD ANI and MND not stated Cognitive decline: 14.5%; stable: 75.5%; improved: 9.1%	No model could predict longitudinal changes in cognitive function	Yes	VBM

All MRI processing/analytical platform were at least semi-automated unless indicated.
N/A: not applicable; ANI: Asymptomatic Neurocognitive Impairment; MND: Mild Neurocognitive Disorder; HAD: HIV-associated dementia; GDS: Global Deficit Score; NP: neuropsychological; ROI: Region of interest; DBM: Deformation-based Morphometry; VBM: Voxel-based Morphometry; TBM: Tensor-Based Morphometry

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Supplemental Digital Content 2. Study MRI Processing details

FreeSurfer Automated Brain Segmentation Steps

In brief, T1-images were motion corrected; intensity normalised; non-brain tissue including the skull and orbits were removed; contours are produced between GM, WM and CSF using intensity gradients to differentiate tissue types; and subcortical WM and deep GM are segmented into relevant neuroanatomical regions (See Figures 1 & 2).

FreeSurfer Output Editing

We conducted conservative manual edits to avoid biasing the FreeSurfer algorithm (McCarthy et al. 2015). Whilst blind to HIV status, all FreeSurfer output was checked for quality of segmentation using the recommended protocol for corrections. Briefly, each slice was inspected in the coronal plane with defects in the surfaces or segmentation that would affect volumes of interest (VOI) verified in all three planes. Errors occurred when voxels were either incorrectly included or excluded in the surfaces or segmentations. Where cerebral WM was incorrectly excluded by the WM surface, control points were added sparingly to manually appoint a WM intensity value of 110 to the excluded voxels. Where voxels were incorrectly labelled in the segmentation, each voxel had to be manually corrected. This occurred most often around the posterior horns of the lateral ventricles, which had been labelled as choroid plexus in approximately 80% of cases. Where areas within the cerebral WM had been incorrectly labelled as cerebral cortex, voxels were re-labelled as WM hyperintensities after confirmation by T2 images.

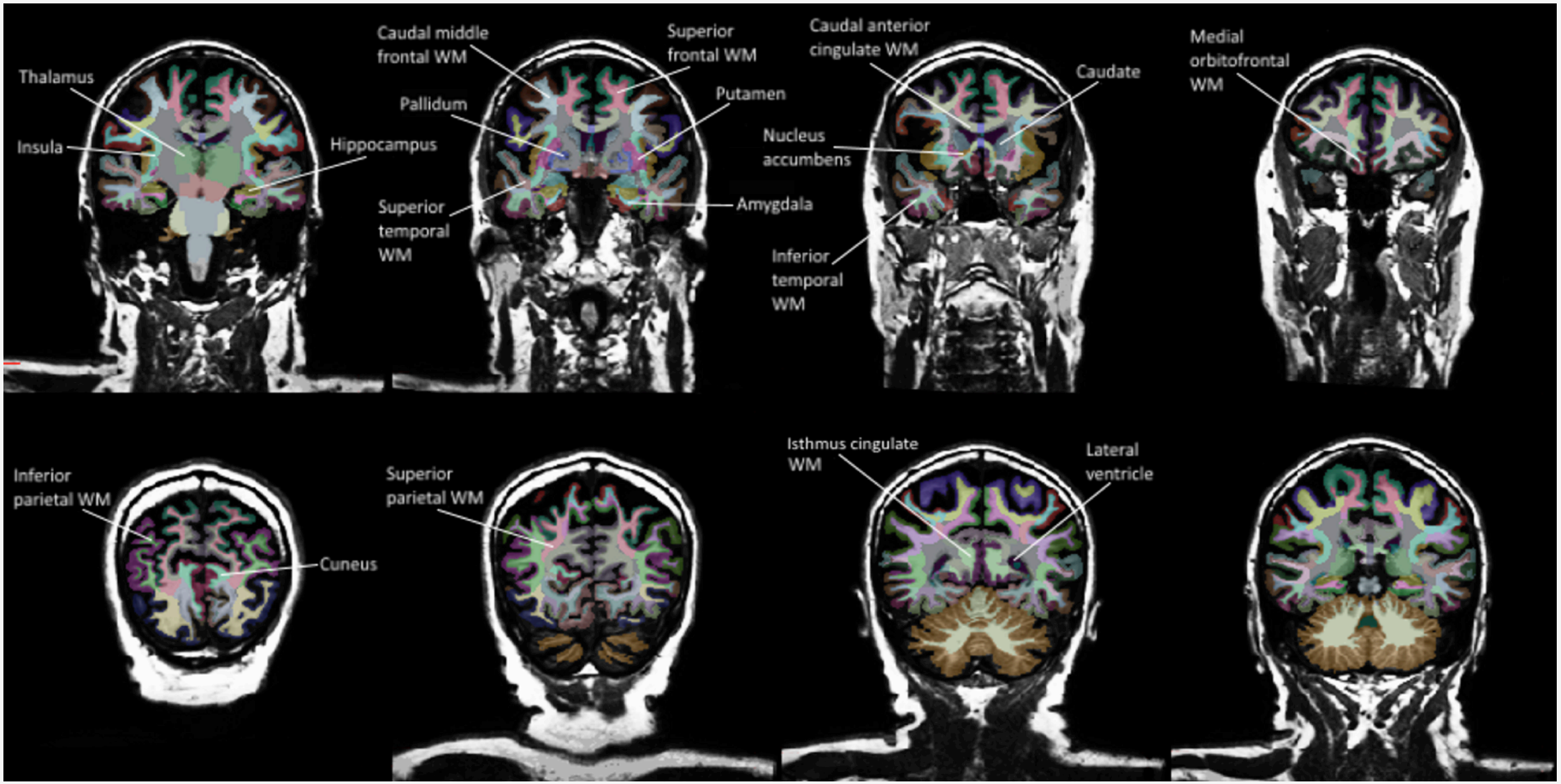


Figure 1. FreeSurfer segmentation of HIV- brain
Example of FreeSurfer segmentation of volumes of interest in coronal MRI slices of an HIV- control.

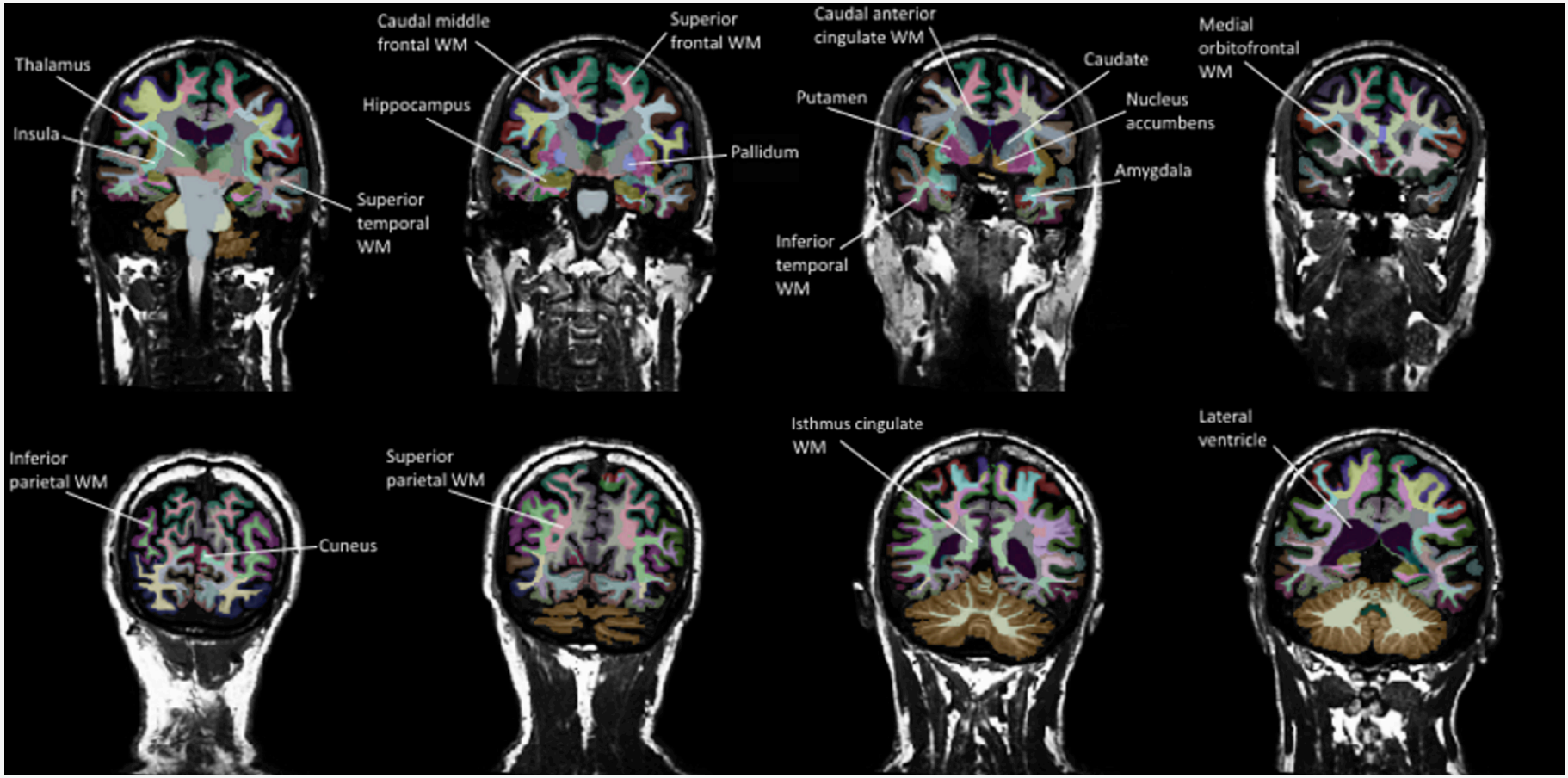
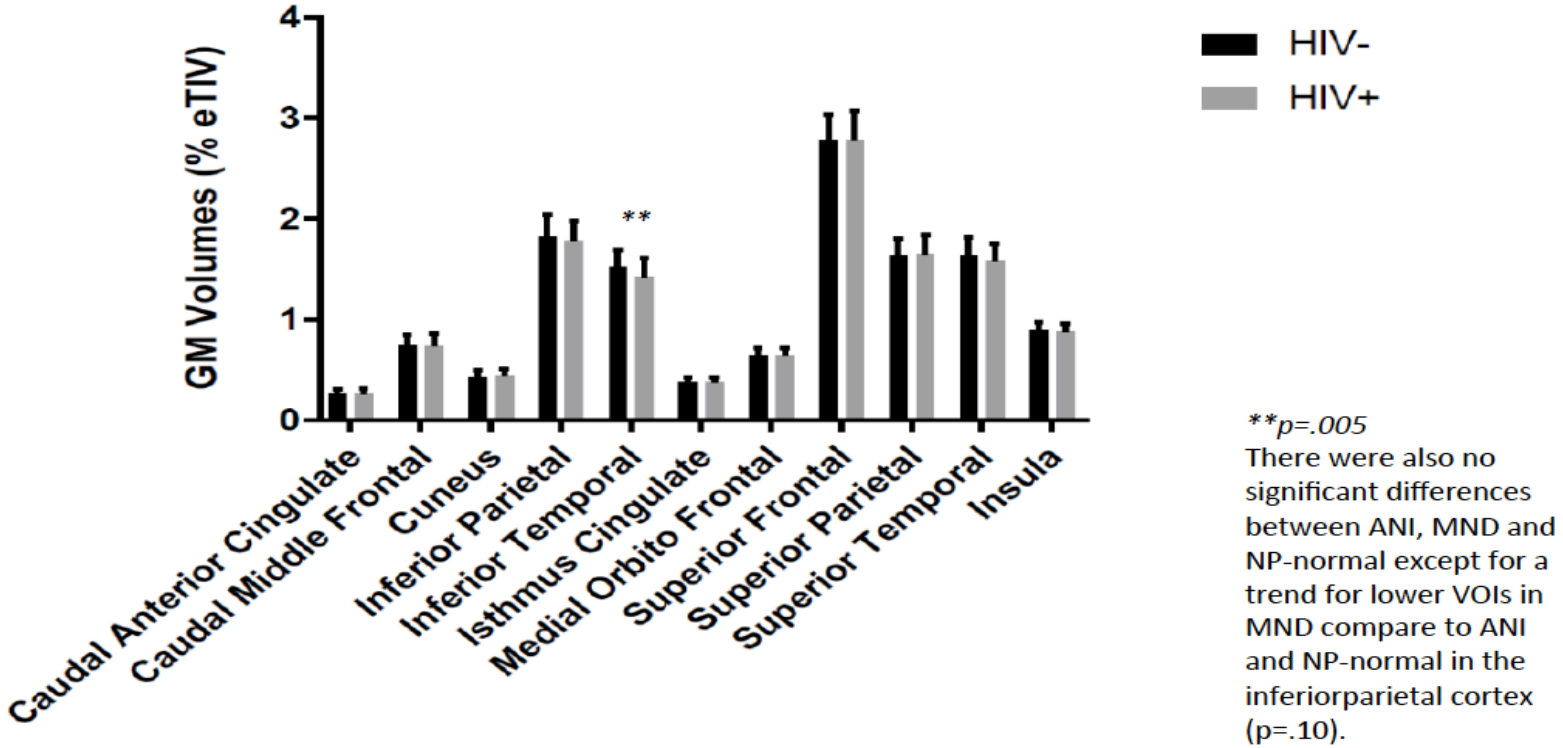


Figure 2. FreeSurfer segmentation of HIV+ brain

Example of FreeSurfer segmentation of volumes of interest in coronal MRI slices of an HIV+ participant.

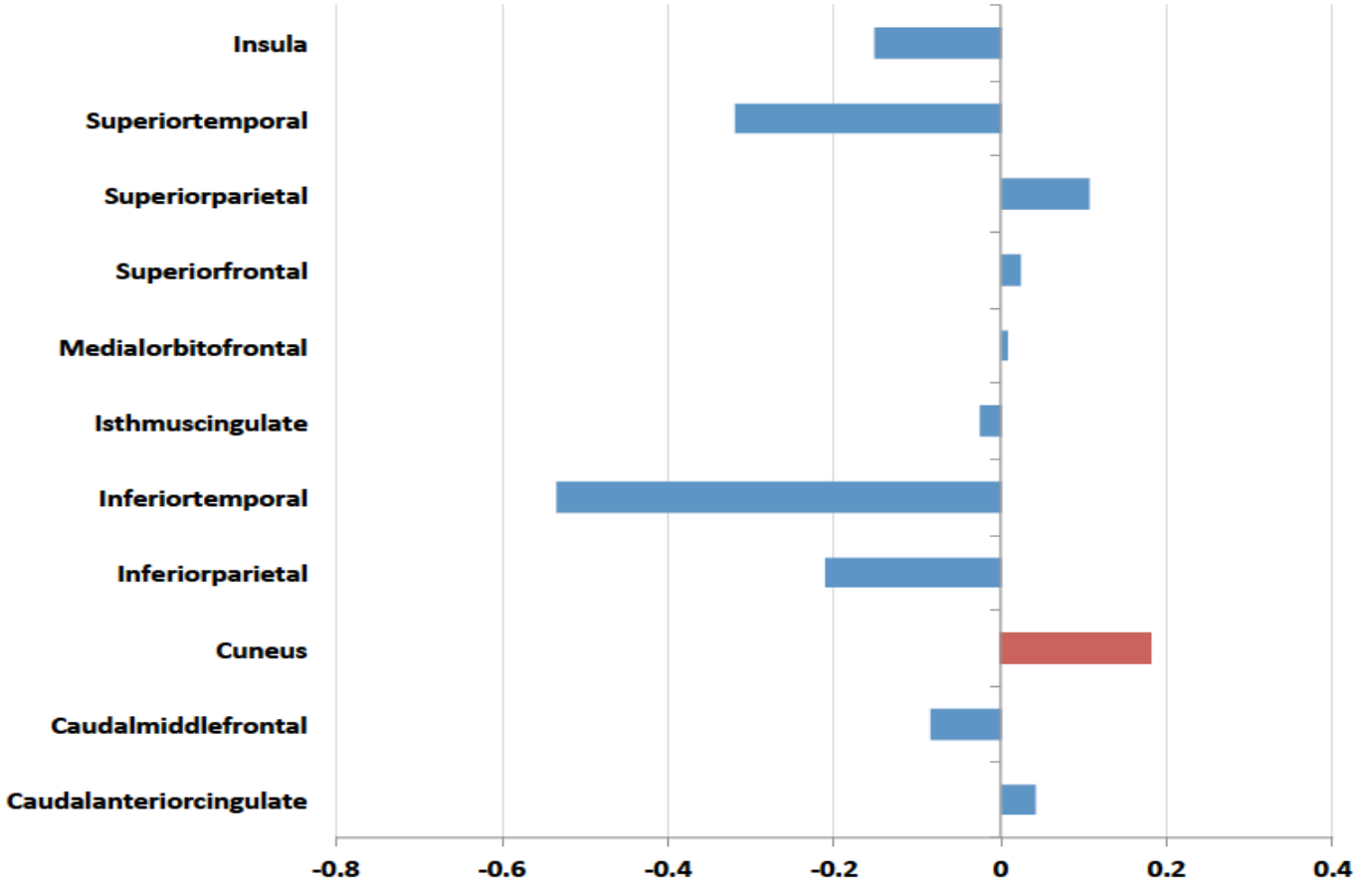
Supplemental Digital Content 3. Cortical parcellation

Supplemental Digital Content 3
Cortical parcellated volumes analyses between the HIV- and HIV+ group
The overall HIV serostatus MANOVA model test was not significant (Pillai's Trace, Wilks' lambda, Hotelling's Trace and Roy's Largest Root $F(11,117)=1.6$; $p=.10$).



***p=.005*
There were also no significant differences between ANI, MND and NP-normal except for a trend for lower VOIs in MND compare to ANI and NP-normal in the inferiorparietal cortex (p=.10).

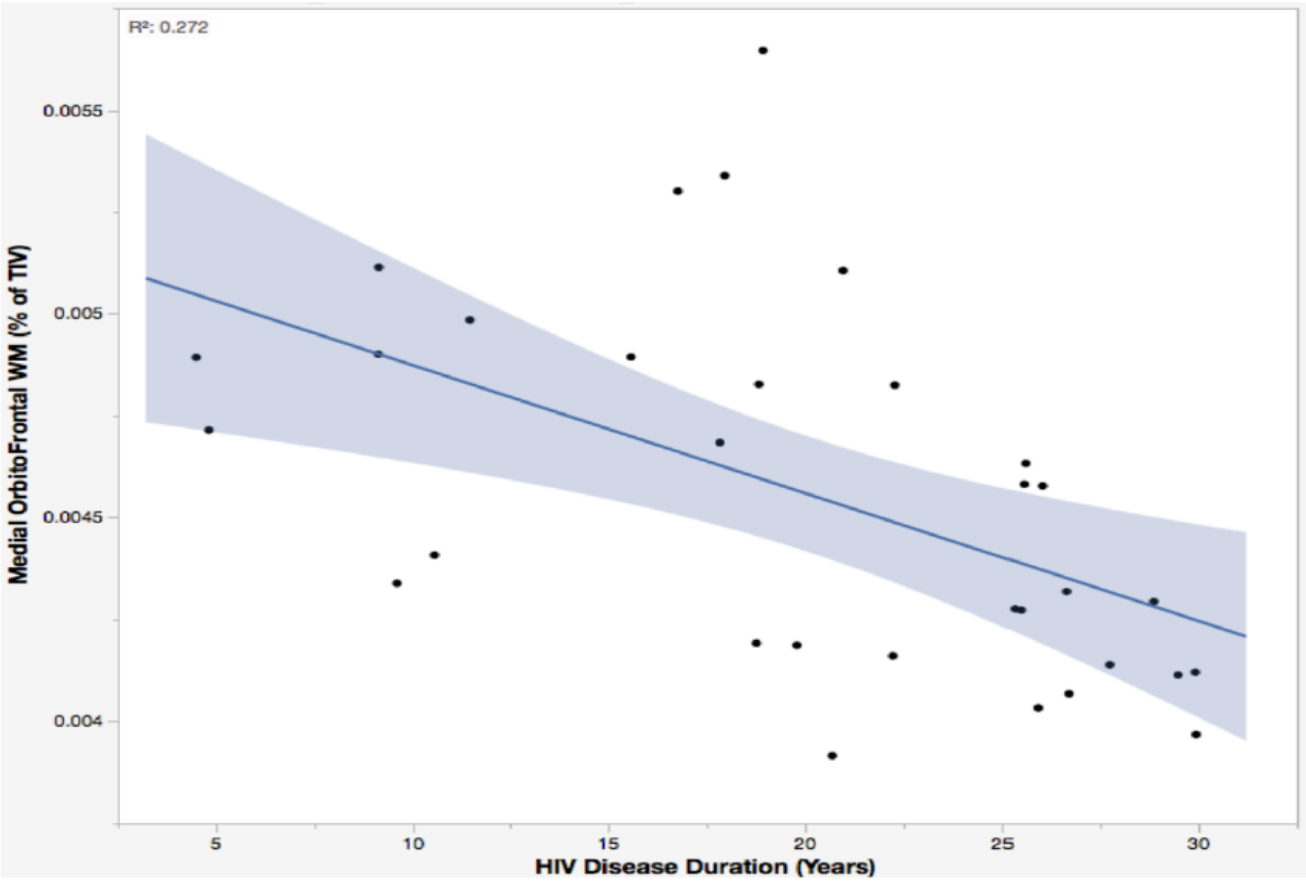
Supplemental Digital Content 3
Cortical parcellated volumes Cohen's d effect size between the HIV- and HIV+ group



Negative effect size indicates smaller volume in HIV+ compared to HIV-

Supplemental Digital Content 4. Biomarkers effects

Figure S1, supplemental digital content 4: HIV duration is uniquely predictive of ANI atrophy on the Medial Orbito-Frontal WM



HIV disease duration uniquely predicted greater medial-orbitofrontal WM atrophy only in ANI (p=.002, β=-.51). Univariate relation is illustrated.

Supplemental Digital Content 4, Table S1

	ANI	**MND**	**NP Normal**	**p_1**	**p_2**	**p_3**
N	32	10	40			
Nadir CD4	192.59 (121.67)	134.80 (121.17)	172.40 (132.63)	0.45	0.75	0.64
Baseline blood CD4	545.13 (316.92)	389.10 (203.90)	580.05 (231.55)	0.13	0.82	0.09
Baseline blood CD8	863.22 (398.37)	955.20 (387.90)	939.75 (398.18)	0.67	0.65	0.99
Baseline logCD4/CD8	-0.52 (0.62)	-0.98 (0.56)	-0.47 (0.64)	0.07	0.92	**0.04**
Baseline HIV duration	20.10 (7.48)	19.56 (5.73)	18.75 (6.41)	0.70	0.64	0.93
AIDS at baseline (%)	68.75	80.00	72.50	-	-	-
Baseline cART duration (months)	39.75 (38.87)	28.90 (21.68)	38.83 (30.90)	0.65	0.99	0.63
History of acute cardiovascular disease (%)[1]	50.00	70.00	42.50	-	-	-
Framingham Score	18.86 (14.28)	19.59 (10.31)	13.80 (7.04)	0.10	0.10	0.24
Baseline D.A.D. score	0.92 (0.45)	0.98 (0.52)	0.74 (0.41)	0.14	0.17	0.23
Baseline CRP	6.39 (18.78)	6.03 (8.64)	6.12 (20.03)	0.10	0.10	0.10

[1] Atrial fibrillation, Myocardial infarction, congestive heart failure, peripheral arteriosclerosis, carotid/coronary arteriosclerosis

p_1 Full Model ANOVA p-value

p_2 NP Normal compared to ANI (Dunnett's control)

p_3 NP Normal compared to MND (Dunnett's control)