A Lower CD4/CD8 Ratio Is Predictive Of Subcortico-Frontal Brain Atrophy In Virally-Suppressed HIV-Infected Persons

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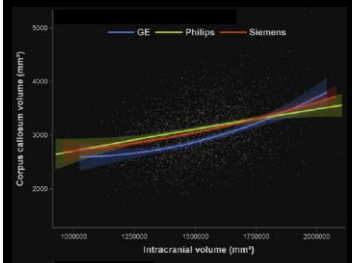
Background

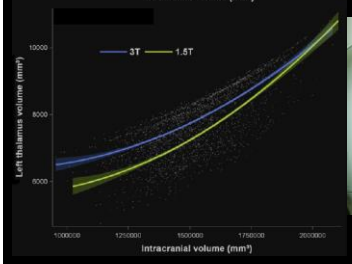
- HIV-related brain damage persists despite viral suppression with cART
- Evidence is based on MRI studies
- However, most studies had limitations so that the magnitude of brain atrophy in virally suppressed HIV+ persons is uncertain and particularly in those with mild neurocognitive impairment
- None extracted a reliable HIV cause to the brain changes except for HIV status difference

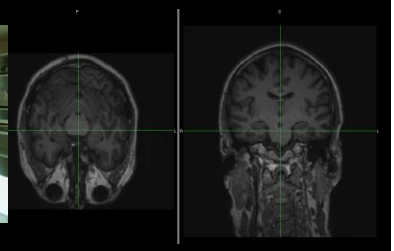
23 Volumetric MRI studies in the cART era

- Only 1/23 was conducted in an entirely virally suppressed cohort
- 14/23 included a HIV- control group, five of these were poorly matched for age, sex and education
- Heterogeneity in segmentation softwares and analytic platforms
- Report of prevalence of cases with HIV-associated neurocognitive disorder was not systematic
- Inclusion of key biomarkers relevant to chronic HIV infection was not consistent

Strength and limitations of Volumetric MRI







Study Aims

- Robustly determine the magnitude and profile of brain atrophy in virally suppressed infection

  1. By focusing on an entirely suppressed HIV+ cohort
  2. By including demographically-comparable HIV- controls
  3. By concentrating on Volumes of Interest (VOI) in specific brain regions known to be affected by HIV including specific WM regions
  4. By quantifying the profile of atrophy in participants with mild form of neurocognitive impairment versus those who were neuropsychologically normal (NP normal)
  5. By assessing the effects of HIV disease biomarkers on atrophic changes.

Participants' demographics

Table 1: Demographic characteristics of the study samples.

	HIV-	HIV+	*p*
N	44	85	
Age (years)	53.9 (6.5)	54.9 (6.5)	.42
Range	45-67	45-69	
Male (%)	100	100	-
Education (years)	15.1 (2.7)	14.0 (2.9)	.05
Range	10-20	8-20	
Urban dwelling MSM (%)	84.1	89.3	.39

Note. MSM = men who have sex with men.

Continuous data presented as Mean (SD) and range unless otherwise specified. Percentage values provided for categorical data

HIV+ participants' clinical characteristics

Table 2: Disease characteristics of HIV+ group

Biomarkers	Median	Range
Median HIV duration (years)	20	4.5-30.6
Median current cART duration (months)	26	6-156
Median nadir CD4 cells/mL	185	0-350
Median current CD4 cells/mL	528	77-1476
CNS Penetration Effectiveness rank score	8 (2.3)	-
Asymptomatic Neurocognitive Impairment (ANI)	38%	-
Mild Neurocognitive Disorder (MND)	13%	-
HIV-associated Dementia (HAD)	3%	-
Historical AIDS (CDC) 1993	71%	-
Plasma HIV RNA undetectable (<50 copies/mL) (%)	98%	-
CSF HIV RNA undetectable CSF (<50 copies/mL) (%)[§]	97%	-

17.6% had a history of HAND

Procedures

- MRI scans on a Phillips 3T scanner: two 3D T1-weighted images & one T2/FLAIR
- Neuropsychological assessment covering 7 cognitive domains, and activities of daily living
- *Laboratory Visit*

HIV-associated Neurocognitive Disorders (HAND)

	Acquired Impairment in ≥2 Cognitive Abilities	Interferes with Daily Functioning	
Asymptomatic Neurocognitive Impairment (ANI)	YES	NO	No Dementia
Mild Neurocognitive Disorder (MND)	YES	MILD	No Dementia
HIV-Associated Dementia (HAD)	MARKED	MARKED	Dementia

Antinori et al., Neurology 2007

NeuRA Discover. Conquer. Cure.

MRI processing

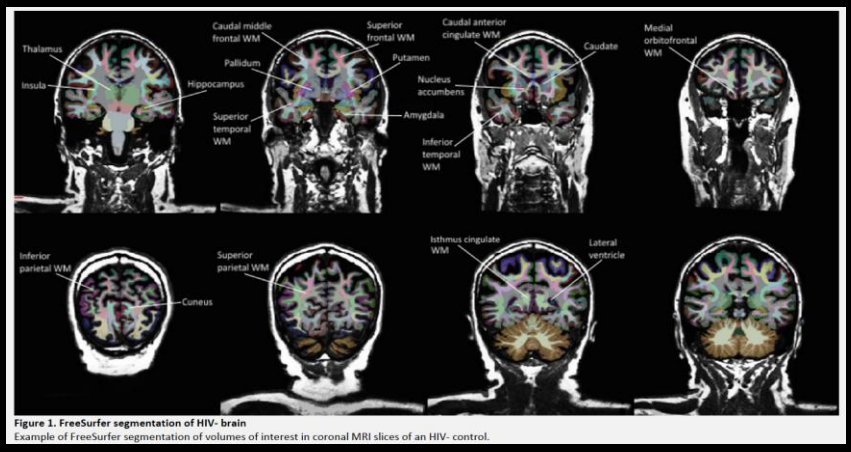
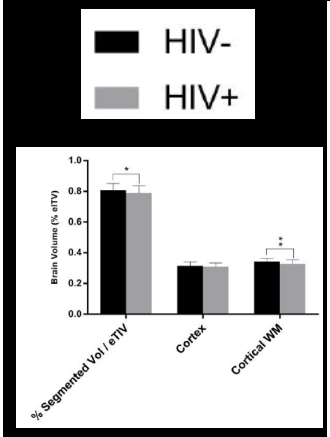
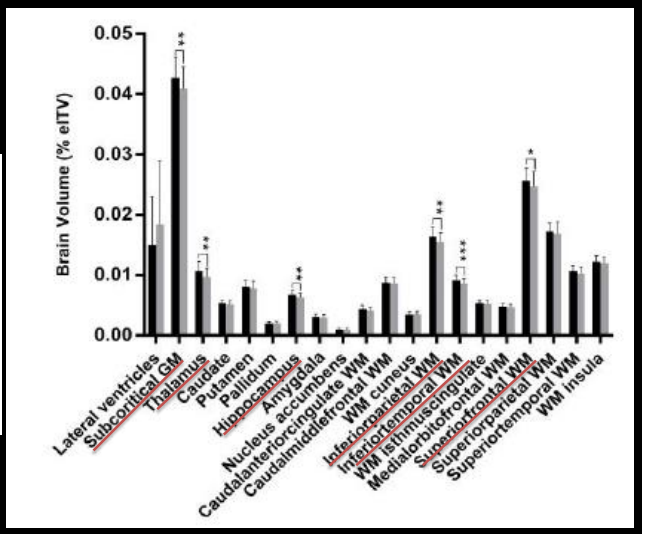


Figure 1. FreeSurfer segmentation of HIV- brain
Example of FreeSurfer segmentation of volumes of interest in coronal MRI slices of an HIV- control.

Volumes of interest (VOI) from MR images were extracted using Freesurfer to yield grey and WM in regions linked to HIV-related brain injury (total cortical volume, basal ganglia, lateral ventricles, fronto-striatal and fronto-parietal WM, **all relative to Total Intracranial Volume, TIV**).

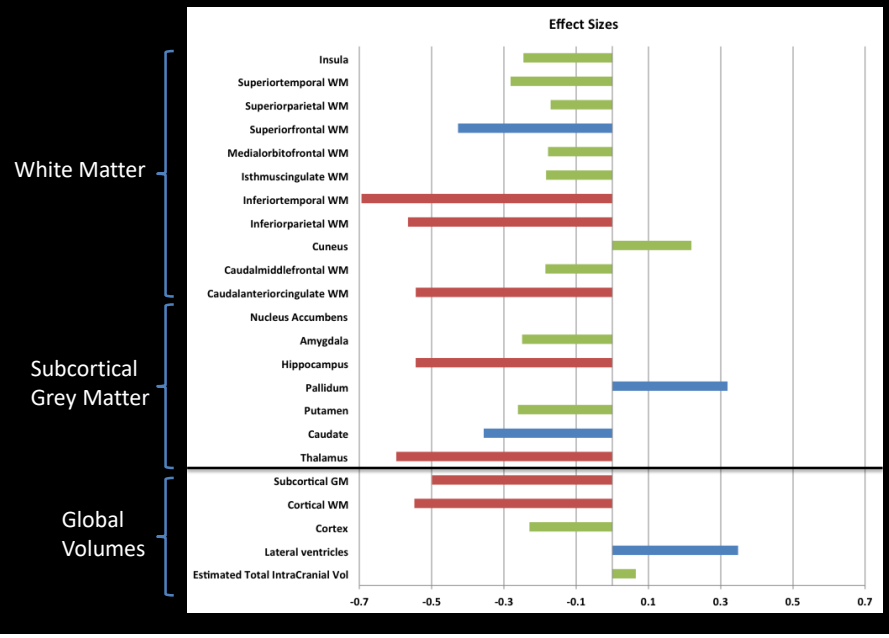
Grey & white matter subcortical atrophy



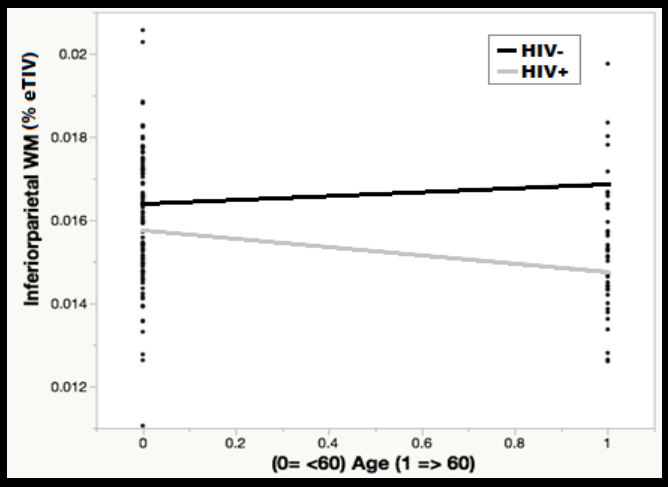


*p<.05; **p<.01; ***p<.001

Magnitude of the atrophy is medium

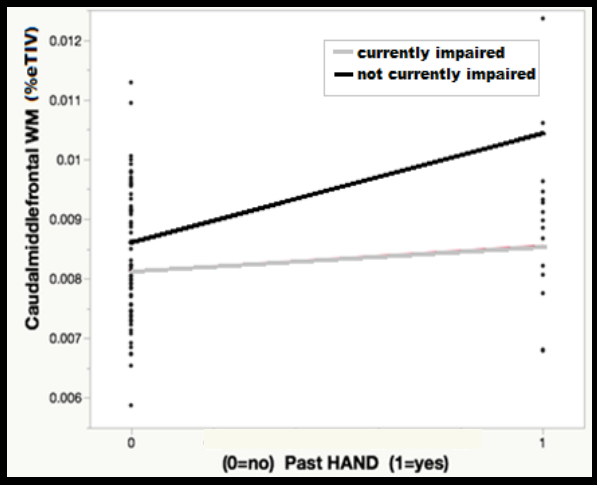


Age and HIV status effect on WM



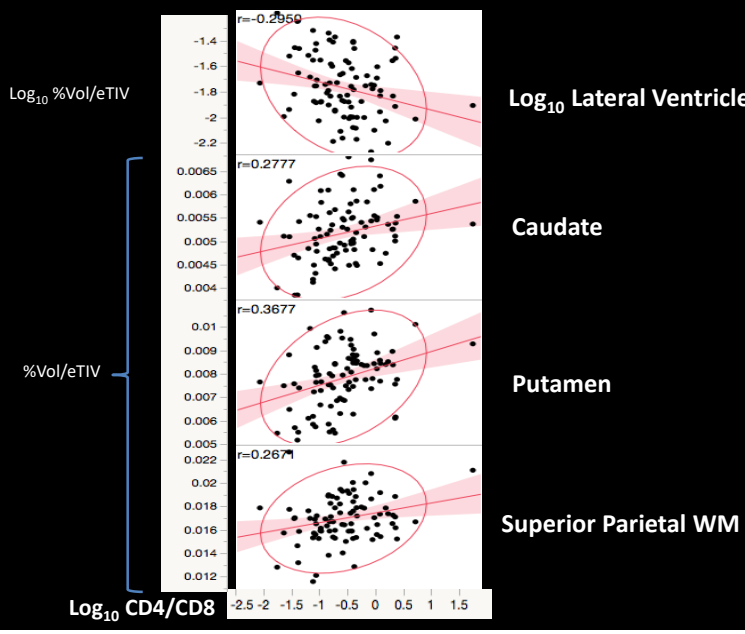
There was a small HIV*age interaction effect for the inferior-parietal WM (p<.02, η^2=.044) indicating that those who were HIV+ and aged 60+ had smaller volumes than cases where only one or neither of these factors were present

Results: Historical and current HAND effect on WM

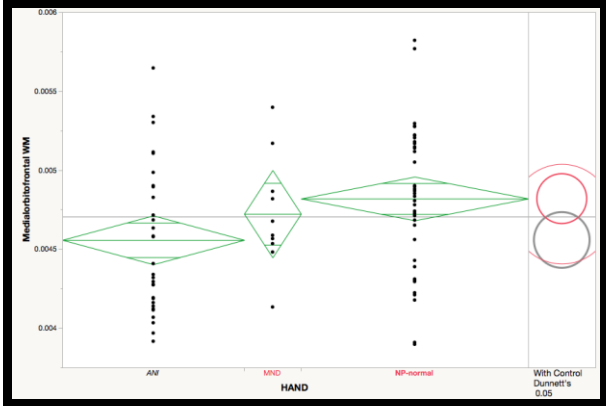


There was a small interaction effect of baseline neurocognitive impairment and historical HAND on caudal-middle-frontal WM (p<.05, η^2=.050) indicating that HIV+ participants with a history of HAND and who were impaired at baseline had smaller caudal-middle-frontal WM volumes than those with only one or neither of these factors were present

CD4/CD8 ratio relates to subcortical atrophy



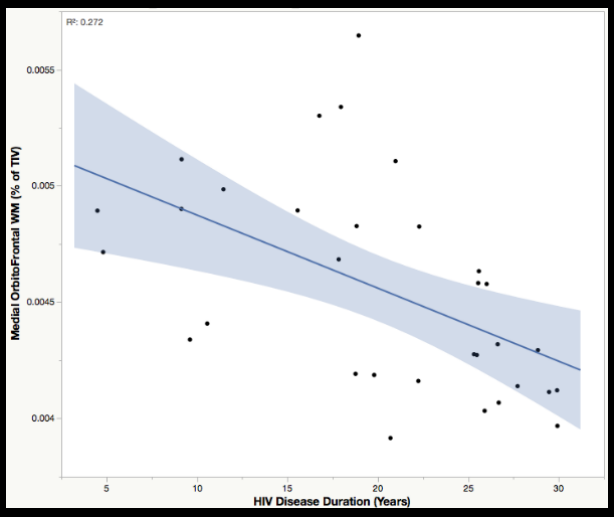
Mild neurocognitive impairment atrophic signature



ANI showed reduced medial-orbitofrontal WM compared to NP-normal cases (p=.04, β=-.31).

MND showed enlarged lateral ventricles (p=.02, β=.34), reduced caudal-middle-frontal WM (p=.04, β=-.32), reduced caudal-anterior-cingulate WM (p=.006, β=-.42), and reduced inferior-parietal WM (p=.04, β=-.33) compared to NP-normal cases.

ANI & HIV duration



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

Conclusions

- A history of HAND explains only small degree of the current atrophy suggesting an *ongoing* neuropathogenic process
- CD8 activation in relation to CD4 level associate with grey subcortical and WM atrophy
- ANI is associated with specific frontal WM atrophy. HIV disease duration a unique contributor to ANI related brain atrophy. These findings give neurobiological validity to ANI and may serve as an ANI biomarker.
- MND atrophic profile was logically more widespread
- Some atrophic volumes had no predictors (e.g., Hippocampus; inferior temporal WM)

Acknowledgements

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