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Long-term Effects of Perinatally-acquired HIV on the Subcortical Shape of The Adolescent Brain

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for the Pediatric HIV/AIDS Cohort Study (PHACS)

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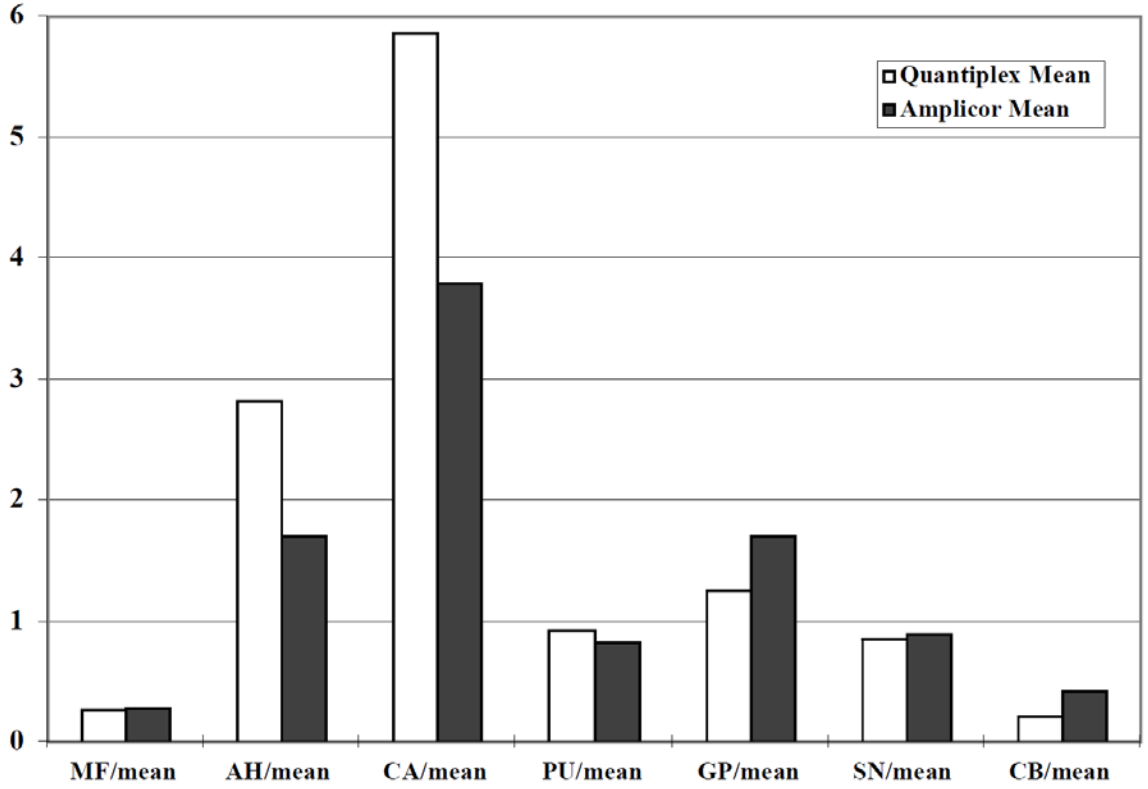
Introduction

Pathology study: differential distribution of HIV RNA load in the brain

HIV RNA Load

QUANTIPLEX™ (clear bar) and AMPLICOR HIV-1 MONITOR™ (dark bar) assays show high viral load in select regions (e.g. caudate nucleus and hippocampus).



MF=mid-frontal cortical
AH=Ammon's Horn
CA=head of caudate
PU=putamen
GP=globus pallidus
SN=substantia nigra
CB=cerebellar cortex

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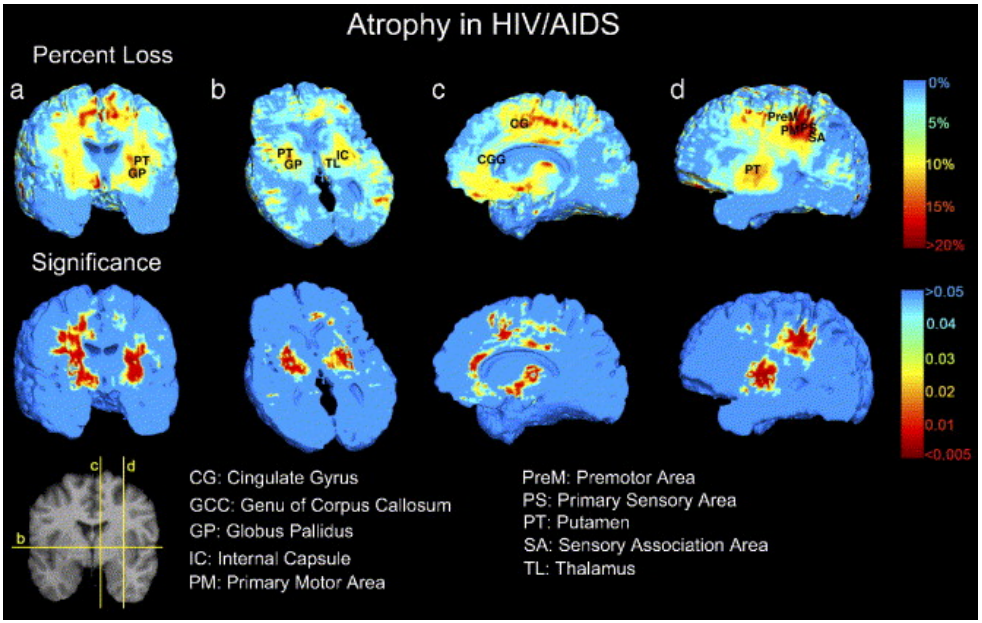
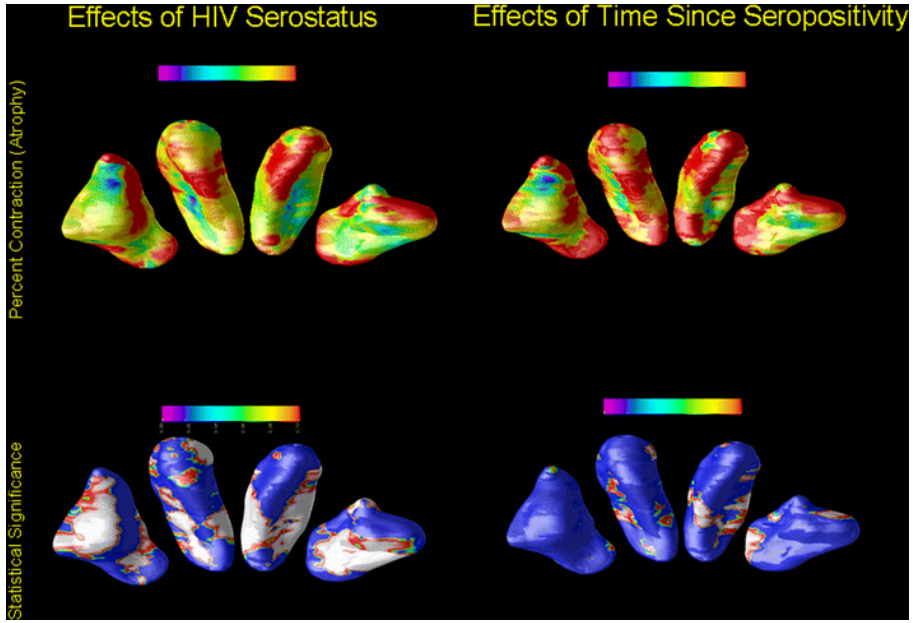
Wiley, C. A., et al. (1998), Distribution of Brain HIV Load in AIDS. Brain Pathology, 8: 277–284. doi: 10.1111/j.1750-3639.1998.tb00153.x

Introduction

Neuroimaging studies: bilateral atrophy in deep nuclei





Bilateral local atrophy in HIV/AIDS

(a) putamen, globus pallidus, (b) thalamus, and in the posterior limb of the internal capsule, along with (c) the cingulate gyrus and the genu and mid-posterior body of corpus callosum, and in (c and d) basal and medial frontal lobes.

Reduction in CDT and PUT in HIV

Top: areas of contraction. The areas of red have no significant contraction, and those with purple have ~15% contraction. Bottom: local significance in the degree of atrophy. Areas marked in white have significant effects (P's < .01).

Chiang, M.-C., et al. (2007). 3D pattern of brain atrophy in HIV/AIDS visualized using tensor-based morphometry. *NeuroImage*, *34*(1), 44–60.

Becker, J. T., et al. (2011). Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging and Behavior*, *5*(2), 77–85.

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Introduction

Our study

- First generation of youths with perinatally-acquired HIV (PHIV), most of whom have received HAART therapy
- Structural MRI of subcortical brain structures
- Primary structures
  - Basal ganglia (caudate, putamen, nucleus accumbens, globus pallidus)
- Secondary structures
  - Thalamus, hippocampus, amygdala
- Measures of HIV disease and cognitive functioning
- Hypothesis: Smaller volumes will be associated with higher HIV measures
- Hypothesis: Shape deformities that correspond to localized volume loss will be associated with higher HIV measures
- Hypothesis: Volume loss & shape deformities will be associated with decreased cognitive performance

Introduction

Covariates

- Age, gender
- Marijuana users have greater volumes in subcortical structures than in control (Gilman, 2014)
- Cannibis use was also associated with shape deformities (Smith, 2014)
- Alcohol abuse is associated with smaller subcortical structures (caudate and putamen) than control subjects (Sullivan, 2005)
- Chronic smoking is associated with global brain atrophy and structural abnormalities compared to non-smokers (Durazzo, 2010)

Methods

Participants

- 40 PHIV youths, 9-18 years
- Ann & Robert H. Lurie Children's Hospital of Chicago, one site of the Adolescent Master Protocol (AMP) study of the PHACS network
- Perinatal infection with HIV as documented in the medical record

Methods

Measures of HIV disease, substance use, and cognitive functioning

- As part of AMP study
- Historical HIV disease severity: the lowest known CD4% ("nadir CD4%") and highest known HIV viral load ("peak viral load") *
- Substance use (alcohol, tobacco, marijuana, illicit drugs)
  - Audio Computer-Assisted Self-Interview, ACASI)
- Cognition
  - Working Memory Index, Processing Speed Index
    - Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV) (6-16 years)
    - Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV) (17+)
  - Cognitive Proficiency Index (CPI)
- Interval between scanning and assessment of current disease markers = 1.8 (3.5) mo
- Interval between scanning and cognitive testing = 0.9 (6.9) mo

* AMP study visits semi-annually through 2010, annually thereafter. At each study visit, CD4 T-lymphocyte percentages (CD4%), plasma HIV RNA concentration (viral load, VL), were abstracted from medical charts.
Smith R, et al. Impact of HIV severity on cognitive and adaptive functioning during childhood and adolescence. Pediatr Infect Dis J. 2012;31(6):592–8.

Methods

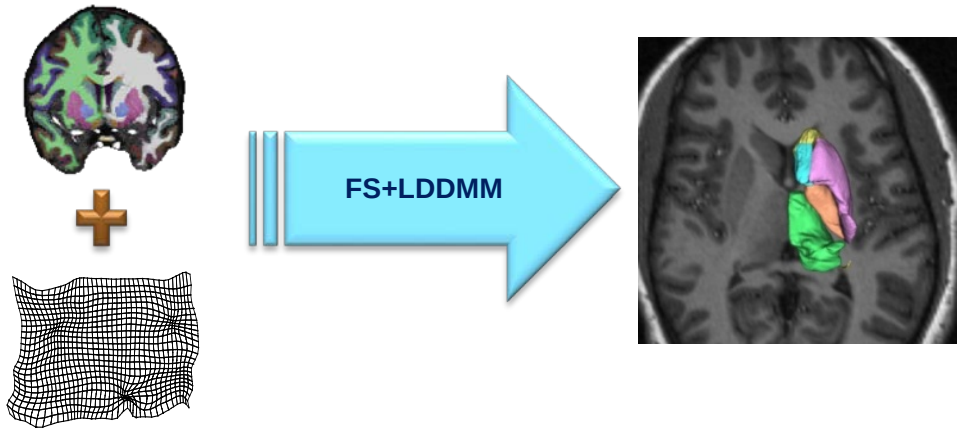
MRI

- Center for Translational Imaging, Northwestern University Feinberg School of Medicine
- Pediatric Imaging, Neurocognition, and Genetics (PING) imaging protocol
- **T1 MPRAGE** (Sagittal, FOV = 256x256mm, TR/TE/TI=2170/2.78/1100, flip angle= 7°, 1 x 1 x 1.2mm^3 resolution). Scan time 8:06 minutes.
- T2 SPACE (Sagittal, FOV=320 mm, TR/TE = 3200/447, 1.0 x 1.0 x 1.0 mm^3 resolution). Scan time 3:52 minutes.
- DTI (Axial, FOV=240mm, TR/TE=9500/91, 2.5 x 2.5 x 2.5 mm^3 resolution, b0=1000, 30 diffusion directions, 68 slices, 2 averages). Scan time 10:00 minutes.
- Resting-state fMRI (Axial, TR/TE=2500/20, flip=80°, 1.72 x 1.72 x 3mm^3 resolution, 36 slices, 170 volumes, parallel to the AC-PC plane). Eyes closed. Scan time 7:05 minutes.

Methods

Image processing

- FS+LDDMM (FreeSurfer-initiated Large Deformation Diffeomorphic Metric Mapping)
  - Atlas-Based Brain Mapping Pipelines
  - FreeSurfer – aligns regions of interest (ROI)
  - LDDMM – accurate and smooth segmentations
  - Fully automated
  - Subcortical surfaces



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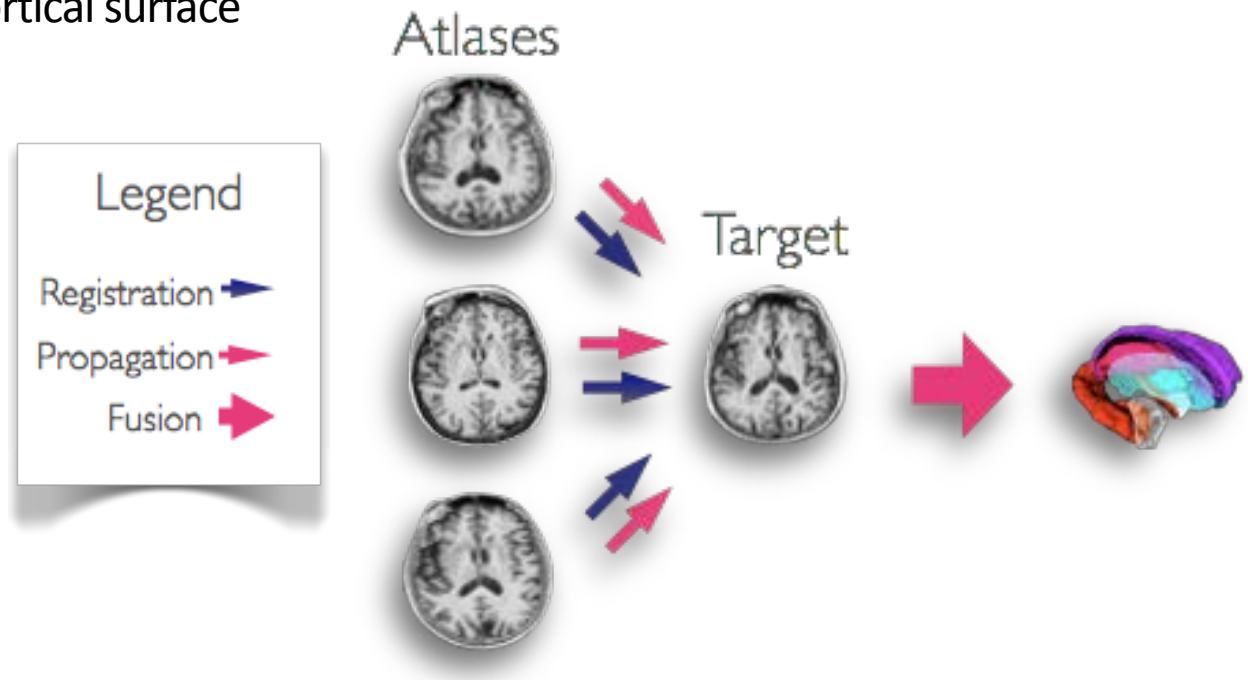
Khan AR, Wang L, Beg MF (2008) NeuroImage. 41:735-746.

Methods

Image processing

- ma-FS+LDDMM (muti-atlas)
  - Register N atlases to the target with single atlas FS+LDDMM
  - Propagate N atlas segmentations to generate N target segmentations
  - Fuse target segmentations via voxel-wise averaging
  - Final subcortical surface

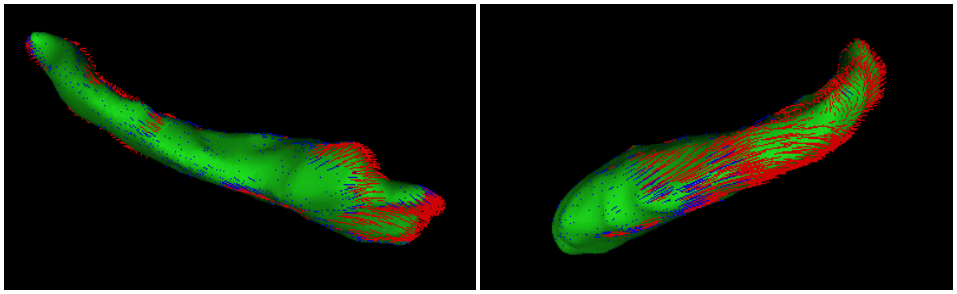


Khan AR, Wang L, Beg MF. IEEE Trans Biomed Eng. 2013 Feb;60(2):544-53.

Methods

Structural variables

- Structural volume
  - Volume enclosed by the subcortical surface
- Structural shape
  - Population average
  - Deformation vectors for all surface vertices (up to tens of thousands)
  - Principal components analysis (PCA) for dimensionality reduction
  - Retain principal components (PCs) that account for ≥75% variance
  - PC scores for each subject's surface will be used for statistical analysis



Methods

Statistical analysis – volume-HIV association

- Dependent measure
  - **Volume**
    - Multivariate GLM, hemisphere modeled as repeated measures
- Predictors
  - **Peak HIV-1 RNA load** (log copies/ml)
  - Age at MRI (log)
  - Age at peak RNA (log)
  - Gender
  - Substance use (total use of alcohol, tobacco, marijuana, illicit drug)
- Primary structures
  - Basal ganglia (caudate, putamen, nucleus accumbens, globus pallidus)
- Secondary structures
  - Thalamus, hippocampus, amygdala

Methods

Statistical analysis – shape-HIV association

- Dependent measure
  - **Surface shape PCs**
    - Multivariate GLM, hemisphere, PCs modeled as doubly multivariate repeated measures
- Predictors
  - **Peak HIV-1 RNA load** (log copies/ml)
  - Age at MRI (log)
  - Age at peak RNA (log)
  - Gender
  - Substance use (total use of alcohol, tobacco, marijuana, illicit drug)
- Primary structures
  - Basal ganglia (caudate, putamen, nucleus accumbens, globus pallidus)
- Secondary structures
  - Thalamus, hippocampus, amygdala

Methods

Statistical analysis – visualization of shape-HIV association

- Dependent measure
  - **Surface deformity vectors**
    - Univariate GLM at each vertex
- Predictors
  - **Peak HIV-1 RNA load** (log copies/ml)
  - Age at MRI (log)
  - Age at peak RNA (log)
  - Gender
  - Substance use (total use of alcohol, tobacco, marijuana, illicit drug)
- Significant structures
  - Visualize vertices $p<0.05$

Methods

Statistical analysis – relationship with cognition

- In structures that show significant association with HIV measures
- Average deformity across the surface (combine left and right)
- Correlate with cognitive proficiency index (CPI)

Results

Subjects

ACASI=audio computer-assisted self-interview; ARV=antiretroviral; PHIV=perinatally HIV-infected, VL=viral load, WISC=Wechsler Intelligence Scale for Children, WAIS=Wechsler Adult Intelligence Scale.

* Illicit drug includes: inhalants, amphetamine, cocaine, methamphetamine, crack, sedatives/barbiturates, ecstasy, hallucinogens, heroin.

** Combination ARV regimen defined as regimen including at least 3 drugs from at least 2 drug classes.

Cognitive Proficiency Index (CPI) = Working Memory Index + Processing Speed Index (WISC-IV, WAIS-IV).

All but 2 subjects completed the age-appropriate Wechsler test within 1 year of the MRI scan, with 31 (77%) being tested within 3 months of brain imaging.

Characteristic	PHIV Youth (N=40)
Age at neuroimaging scan (years), mean (SD)	16.7 (2.4)
Sex	
Male	19 (48%)
Female	21 (53%)
HIV Disease Severity Measures	
Nadir CD4%	16.5 (8.0, 23.8)
Nadir CD4% < 15%	17 (43%)
Age at nadir CD4%	5.7 (2.2, 10.9)
Most recent CD4%	35.9 (27.6, 42.9)
Age at most recent CD4%	17.0 (14.9, 18.2)
Log peak HIV RNA viral load (copies/mL)	5.7 (5.2, 5.9)
Age at peak RNA (years)	2.5 (0.6, 5.3)
Most recent RNA count > 400 copies/mL	6 (15%)
Age at most recent RNA (years)	17.0 (14.9, 18.2)
% of VL > 1000 copies/mL in past 5 years	6.5 (0.0, 29.0)
Substance use by ACASI	
Alcohol	14 (35%)
Tobacco use	10 (25%)
Marijuana use	14 (35%)
Illicit drug use excluding marijuana *	3 (8%)
ARV regimen at the time of brain scanning	
Combination ARV regimen**	37 (92%)
Not on combination ARV regimen	1 (3%)
Not on any ARVs	2 (5%)
WISC/WAIS evaluation measures (mean, SD)	
Cognitive Proficiency Index	90.3 (16.0)
Working Memory Index	87.6 (16.8)
Processing Speed Index	95.4 (14.2)
Age at evaluation, years (median, IQR)	16.8 (15.2, 18.0)

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Methods

Statistical analysis

- Dependent measure
  - **Morphometry** (volume, surface shape PC, surface deformity vectors)
    - Multivariate GLM
- Predictors
  - **Peak HIV-1 RNA load** (log copies/ml)
  - Age at MRI (log)
  - Age at peak RNA (log)
  - Gender
  - Substance use (total use of alcohol, tobacco, marijuana, illicit drug)
- Primary structures
  - Basal ganglia (caudate, putamen, nucleus accumbens, globus pallidus)
- Secondary structures
  - Thalamus, hippocampus, amygdala

Results

Volume

- Dependent measure
  - **Volume**
    - Hemisphere modeled as repeated measures
- Predictors
  - **Peak HIV-1 RNA load**
  - Age at MRI
  - Age at peak RNA
  - Gender
  - Substance use

Volume	F (1, 32)	P
Caudate	1.19	0.28
Putamen	2.88	0.10
Accumbens	0.11	0.74
Pallidum	1.42	0.24
Thalamus	1.77	0.19
Hippocampus	0.00	0.98
Amygdala	0.03	0.87

No hemisphere-by-peak RNA load interaction

Results

Shape

- Dependent measure
  - **Surface shape PC**
    - Shape PCs modeled as doubly multivariate repeated measures
- Predictors
  - **Peak HIV-1 RNA load**
  - Age at MRI
  - Age at peak RNA
  - Gender
  - Substance use

Shape PC	F	df	P
Caudate	**3.09**	**(4, 29)**	**0.031**
Putamen	1.69	(6, 27)	0.16
Accumbens	0.58	(5, 28)	0.72
Pallidum	**2.65**	**(6, 27)**	**0.038**
Thalamus	2.39	(6, 27)	0.056
Hippocampus	0.41	(3, 30)	0.75
Amygdala	0.05	(4, 29)	0.99

No hemisphere-by-peak RNA load interaction

Results

Shape visualization

- Dependent measure
  - **Surface deformity vectors**
    - Surface deformity performed at every vertex, uncorrected p<0.05
- Predictors
  - **Peak HIV-1 RNA load**
  - Age at MRI
  - Age at peak RNA
  - Gender
  - Substance use

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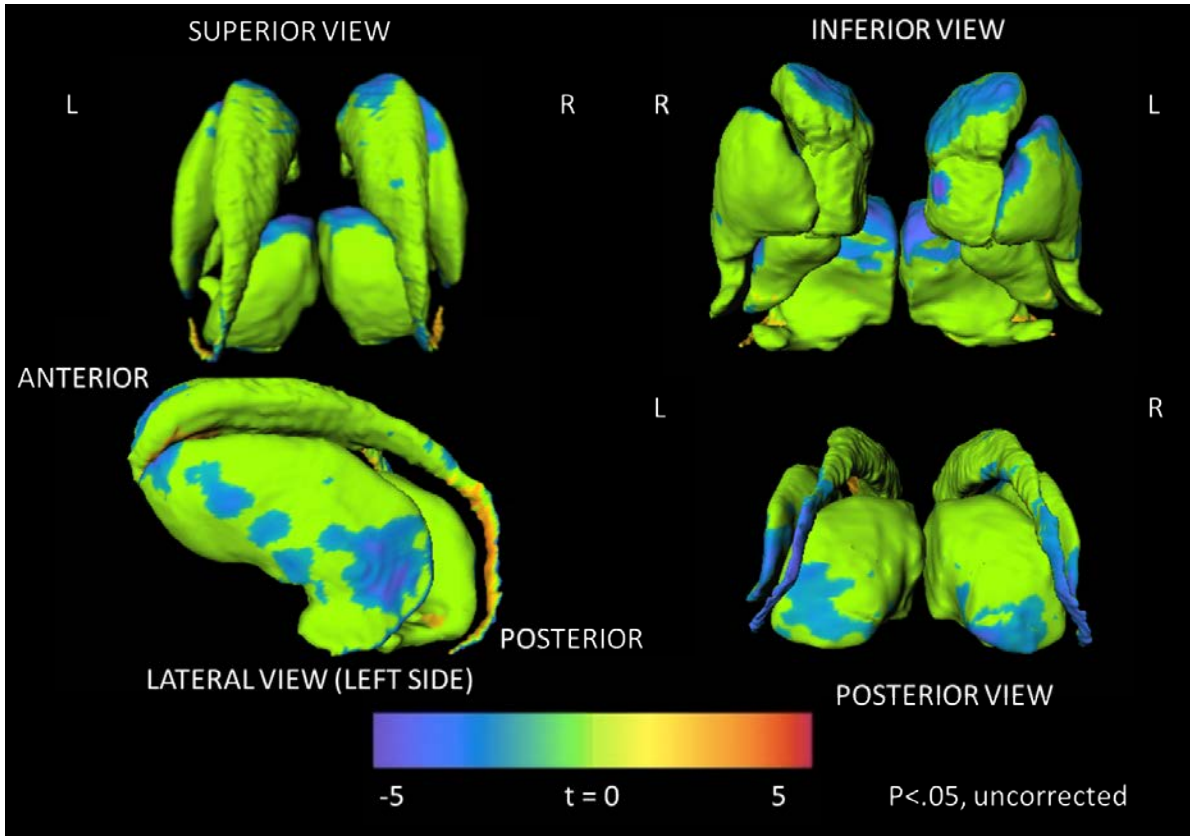
basalganglia_rl5_wi

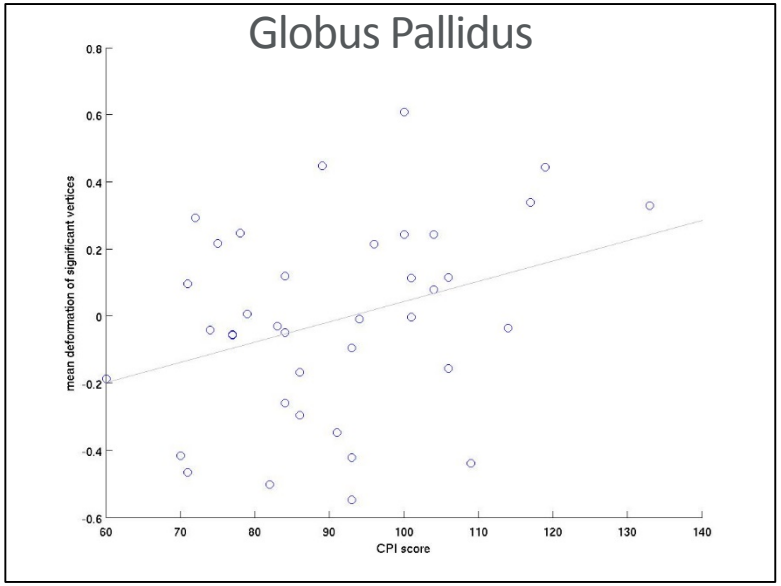


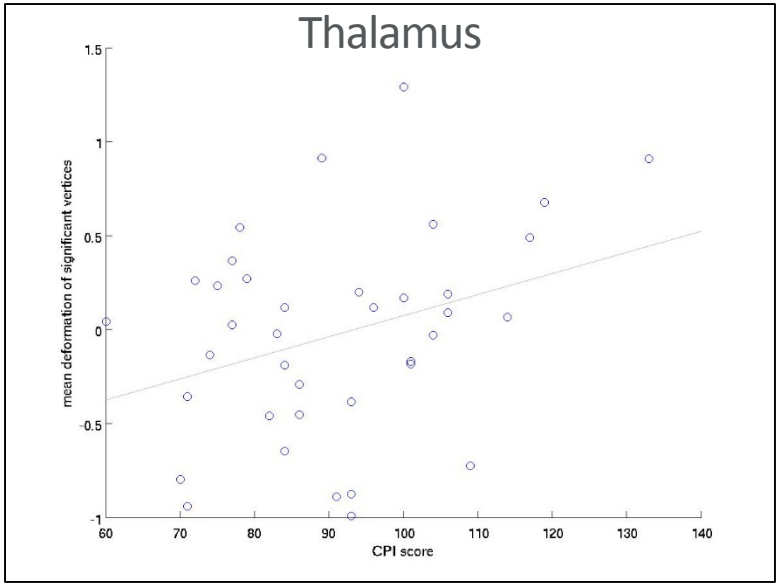
Results

Correlate with cognition

- Dependent measure
  - **Average surface deformity vectors**
- Predictors
  - **Cognitive Proficiency Index**

	r	P
Caudate	0.25	0.07
Putamen	0.31	0.06
Pallidum	**0.33**	**0.04**
Thalamus	**0.33**	**0.04**





Inward deformity (volume loss)⟷Lower CPI

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Results

Correlate with cognition

- Dependent measure
  - **Average surface deformity vectors**
- Predictors
  - **Cognitive Proficiency Index**

	r	P
Caudate	0.25	0.07
Putamen	0.31	0.06
Pallidum	**0.33**	**0.04**
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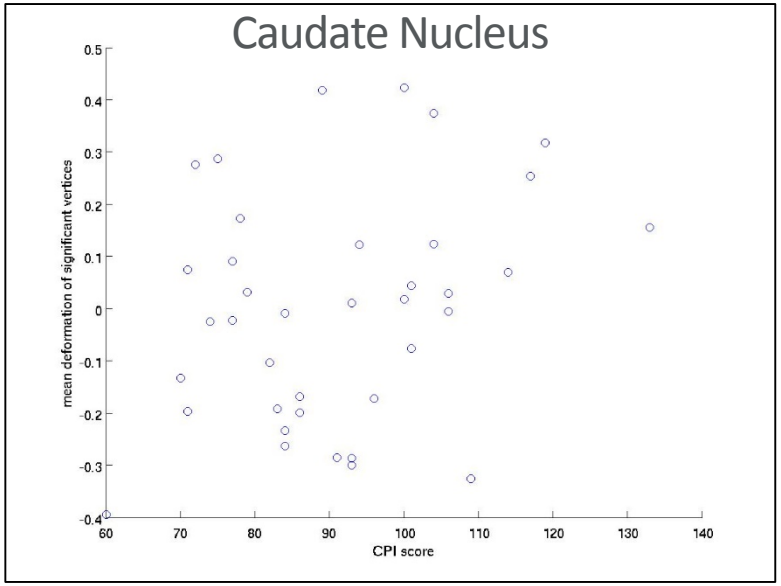

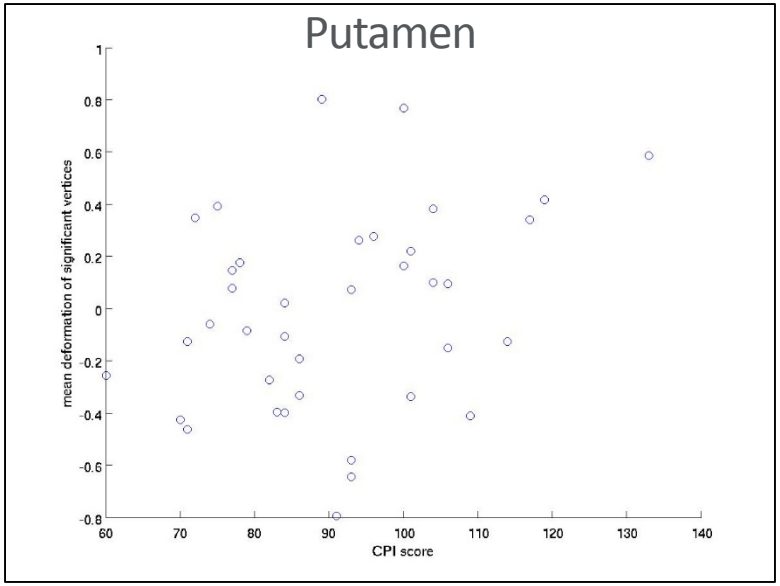

Inward deformity (volume loss)⟷Lower CPI

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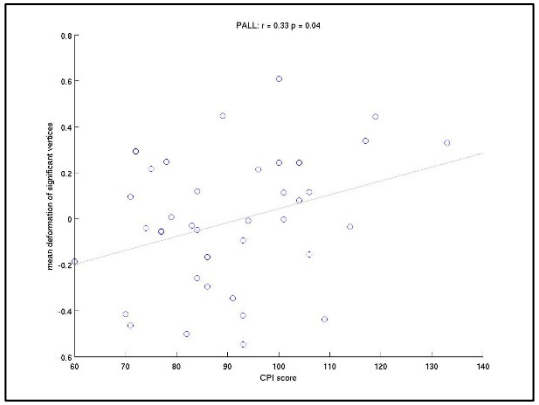
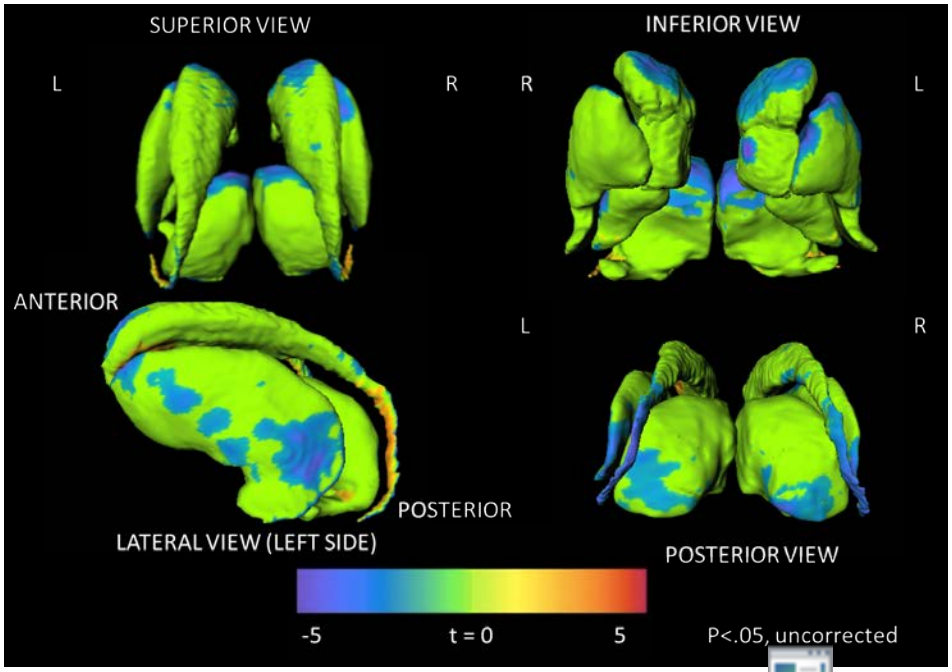
Summary

Peak HIV viral load

- In PHIV youth, higher peak viral load was associated with greater localized volume loss in the basal ganglia regions, (thalamus), not in hippocampus.
- These losses were associated with lowered cognitive proficiency index.
- Our findings are consistent with histopathologic and clinical studies in adults with HIV.
- Our findings suggest that patterns of brain dysmorphology in adolescents with life-long HIV given antiretroviral therapy during brain development are similar to those in adult studies.





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basalganglia_rl5_wi

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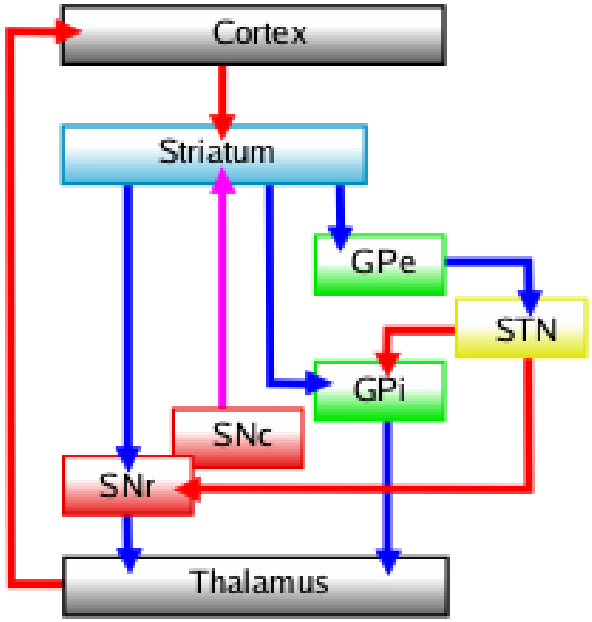
Summary

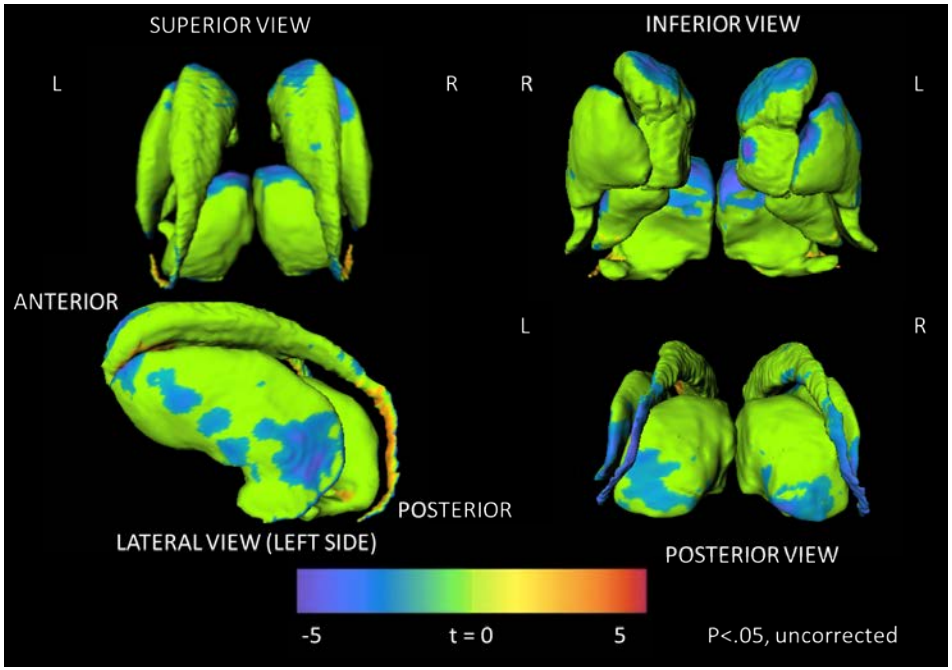
Nadir CD4%

- No association with nadir CD4 lymphocyte percentage was observed.

Discussion



- Direct pathway: cortex -> GPi -> thalamus <-> cortex
  - The direct pathway combines the '-' inhibitory signal coming from the striatum, and the '-' inhibition signal coming from GPi, and send "disinhibition" signal to the thalamus.
- Indirect pathway: cortex -> GPe -> GPi -> thalamus <-> cortex
  - The indirect pathway adds an extra '-' inhibition to the disinhibition of the direct pathway, and send "inhibition" to the thalamus.



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basalganglia_rl5_wi

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- Patients and families
- NIH/PHACS
  - Paige L. Williams, Yanling Huo, Kathleen Malee, Russell B. Van Dyke
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