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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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
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).

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

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 1.2mm³ resolution). Scan time 8:06 minutes.
• **T2 SPACE** (Sagittal, FOV=320 mm, TR/TE = 3200/447, 1.0 x 1.0 x 1.0 mm³ resolution). Scan time 3:52 minutes.
• **DTI** (Axial, FOV=240mm, TR/TE=9500/91, 2.5 x 2.5 x 2.5 mm³ 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 3mm³ 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

**Methods**

**Image processing**

- ma-FS+LDDMM (multi-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

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 $\geq 75\%$ 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

- 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.
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

<table>
<thead>
<tr>
<th>Volume</th>
<th>F (1, 32)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caudate</td>
<td>1.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Putamen</td>
<td>2.88</td>
<td>0.10</td>
</tr>
<tr>
<td>Accumbens</td>
<td>0.11</td>
<td>0.74</td>
</tr>
<tr>
<td>Pallidum</td>
<td>1.42</td>
<td>0.24</td>
</tr>
<tr>
<td>Thalamus</td>
<td>1.77</td>
<td>0.19</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>0.00</td>
<td>0.98</td>
</tr>
<tr>
<td>Amygdala</td>
<td>0.03</td>
<td>0.87</td>
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</tbody>
</table>

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

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

Correlate with cognition

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

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<tbody>
<tr>
<td>Caudate</td>
<td>0.25</td>
<td>0.07</td>
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<tr>
<td>Putamen</td>
<td>0.31</td>
<td>0.06</td>
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<tr>
<td>Pallidum</td>
<td>0.33</td>
<td>0.04</td>
</tr>
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<td>Thalamus</td>
<td>0.33</td>
<td>0.04</td>
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Inward deformity (volume loss) $\rightarrow$ Lower CPI
Results

Correlate with cognition

- Dependent measure
  - Average surface deformity vectors

- Predictors
  - Cognitive Proficiency Index

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Inward deformity (volume loss) $\leftrightarrow$ Lower CPI
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.
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.

![Diagram showing the direct and indirect pathways in the basal ganglia](image)
Acknowledgement

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