Impaired Cognition and Reduced Brain Volumes in Youth with Behaviorally Acquired HIV

Jennifer McGuire MD MSCE[1,4], Robert Brown PhD[5], Ritobrato Datta PhD[1,4], Giulia Fadda MD[4], Nichole Tuite BA[1], Jacqueline Harrison BA[1], Steven D Douglas MD[2,3], Brenda Banwell MD[1,4]
Divisions of [1]Neurology, [2]Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA; Departments of [3]Pediatrics, and [4]Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA; [5]ShadowLab Research Inc., Toronto, Canada.

Background

- Behaviorally acquired (non-perinatal) HIV infection during adolescence and young adulthood occurs during key brain developmental processes, including frontal lobe pruning and network selection.
- Up to 50% of adults with HIV demonstrate cognitive impairment in the combined antiretroviral therapy era
  - Higher impairment correlates with lower cortical and subcortical volumes on neuroimaging and neuropathologic studies, greater viral burden, and lower lifetime CD4+ T-cell nadirs[1-5]
  - Comparable data in adolescents and young adults with behaviorally acquired HIV are sparse, but executive and motor function may be impaired in up to 65%[6,7]. .
    - There are no neuroimaging studies of adolescents/young adults
- Our pilot data demonstrate lower deep gray volumes in HIV+ youth compared to historical controls.

Objective/Methods

OBJECTIVES

- Determine the difference in deep gray structural volumes between adolescents/young adults with behaviorally acquired HIV, and age-, sex-, demographic-, and risk-factor matched uninfected controls, using MRI structural morphometry
- Identify possible secondary risk factors for lower striatal volumes among HIV+ and control youth.

STUDY DESIGN

- Cross sectional analysis of 16-20 year-old Philadelphia youth
  - **Inclusion:** Natal males and females, any race/ethnicity, English speaking. HIV+ youth must be infected for ≥1 year, after age 9.
  - **Exclusion**: Pregnant or lactating females; current (or past) use of exogenous sex hormones; known cognitive impairment or psychosis (present prior to HIV infection for HIV+ youth); use of chronic steroids; contraindications to MRI; conditions other than HIV that could potentially impact cognitive testing or neuroimaging.
- MRI performed on Siemens 3T Prisma.
- Serum cytokines measured by Luminex- magnetic bead based assay.
- Cognitive impairment defined by "Global Deficit Score" (GDS) ≥ 0.5[9]; HIV-associated neurocognitive disorder (HAND) defined by Frascati criteria[10].

STATISTICAL ANALYSIS

- FreeSurfer v5.3 (Harvard University, Boston, MA) was used to measure whole structure volumes. Stata v14.0 (StataCorp, College Station, TX) was used for all analysis except voxel-based analysis.
- Voxel-based volume differences relative to distance from CSF interface between study participants and a standard age-matched atlas were calculated using deformation based morphometry and nonlinear mixed effects modeling with ANTs, custom Python code, and R.
- p-values comparing intergroup differences calculated using χ^2 tests for categorical and Wilcoxon rank sum tests for continuous variables

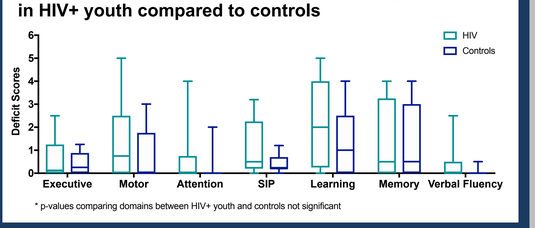
Selected References:
1. Ances et al. *Curr Opin HIV AIDS* (2014) 9:545-551
2. Price et al. *Neurology* (2007) 69: 1781-1788
3. Paul et al. *Neurosci Biobehav Rev* (2002) 26:353-359
4. Paul et al. *J Int Neurospycol Soc* (2008) 14:725-733.
5. Ances et al. *J Acquir Immune Defic Syndr* (2012) 59:469-477
6. Nichols et al. *J Adolesc Health* (2013) 53:763-771
7. Baker et al. *J Neurovirol* (2014) 20: 466-473
8. McGuire et al *ANA Career Devel Symposium* (2016)
9. Carey et al. *J Clin Exp Neuropsychol* (2004) 26(3): 307-319
10. Antinori et al. *Neurology* (2007) 69(18): 1789-1799

Table 1: Demographics and Clinical Characteristics of the Study Population

Characteristic	HIV+ (n=17)	Controls (n=18)	p-value
Male sex, n	16 (94)	17 (94)	0.97
Black race, n	15 (88)	17 (94)	0.58
Age, years	20.0 (18.9, 20.7)	19.5 (18.5, 20.6)	0.55
Medicaid	11 (69)	11 (65)	0.38
HIV sexual risk factors	13 (76)	13 (72)	0.77
ACES (n=14; n=8 HIV+, n=6 control)	3.5 (1.5, 5.5)	5.5 (3,7)	0.24
CES-D	6 (4,12)	24 (11,29)	<0.001
Prior syphilis infection (no current)	10 (59)	1 (6)	0.001
Hepatitis C Virus +, n	0 (0)	0 (0)	-
Average alcohol per week, # drinks	0 (0,1)	0 (0,1)	0.71
Average marijuana per wk, # serving	5 (0,14)	1 (0,5)	0.16
Currently using cART	17 (100)	-	-
Ever use PREP	-	7 (39)	-
Cognitive Data			
Education, years	12 (11, 13)	12 (11, 13)	0.68
Maternal Education (n=30)	12 (12, 14)	13 (12, 14)	0.44
WRAT4	83.5 (76,93.5)	92 (82,98)	0.19
MOCA score[a]	23.5 (20, 26)	27 (25,28)	**0.037**
Global Deficit Score (GDS) ≥ 0.5[a]	11 (69)	10 (59)	0.55
Meets HAND criteria	11 (69)	8 (47)	0.21
Laboratory Data (plasma)			
IFN-γ	6.8 (6.5,8.1)	6.3 (5.9,6.8)	**0.009**
IL-1β	0.5 (0.5, 0.6)	0.6 (0.5,0.7)	0.35
IL-6	1.0 (0.8,1.3)	1.0 (0.9,1.3)	0.75
IL-8	12.5 (10.9,16.0)	9.5 (6.1,15.2)	0.16
IL-10	1.7 (1.5,2.2)	1.6 (1.4,2.1)	0.73
TNF-α	11.3 (10.3,14.0)	10.5(9.4,12.5)	0.28
Serum NFL	3.6 (3.2,4.6)	3.5 (3.1,5.0)	0.83
HIV+ Subjects:			
Infection duration, years	1.9 (1.4, 2.9)	-	-
CD4+ nadir, cells/uL	410 (323, 478)	-	-
CD4+ nadir ≤200, n	2 (12)	-	-
Plasma CD4+, cells/mm^3	619 (410, 740)	-	-
HIV-1 RNA ,≤30 copies/mL, n	15 (88)	-	-
31-10,000, n	2 (12)	-	-
10,000-99,999, n	0 (0)	-	-
≥100,000, n	0 (0)	-	-
Not reported, n	2 (12)	-	-

Categorical variables are described using n (%).
Continuous variables are described using median (intraquartile range).
[a] Cognitive data available for 33 total subjects: 16 HIV+ and 17 controls

Figure 1: Cognitive testing deficit scores may be lower in HIV+ youth compared to controls



* p-values comparing domains between HIV+ youth and controls not significant

Supported by the NINDS: K23 NS094069

Figure 2: Thalamus and caudate volumes may be lower in HIV+ compared to controls, while total intracranial volume is the same (data not shown).

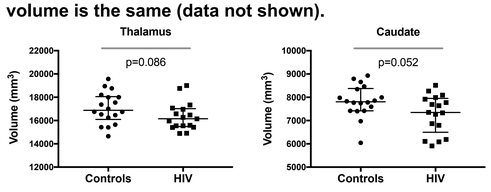


Figure 3: Volume differences between HIV (n=12) and controls (n=14) of thalamus and caudate are most pronounced proximal to CSF surface

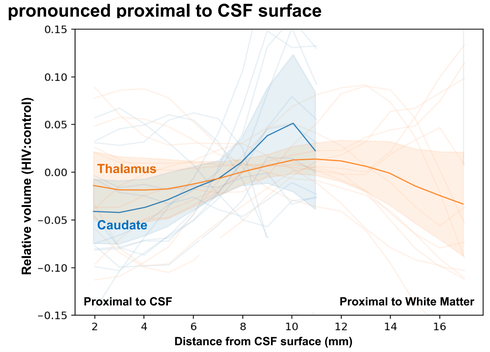
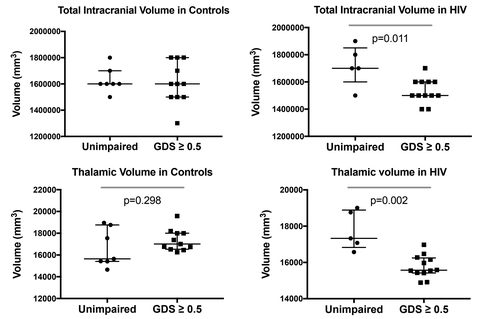


Table 2: Univariate Analysis of Factors Associated with Lower Caudate Volumes (cm^3)

	coefficent	95% Confidence Interval	p-value
HIV+ status	-0.55	-1.07, -0.03	**0.039**
ACES score	0.03	-0.19, 0.26	0.74
CES-D	0.02	0.00, 0.05	0.08
Education	0.17	-0.04, 0.38	0.11
Average # alcohol/week	0.04	-0.10, 0.19	0.58
Average # marijuana/week	0	-0.03, 0.03	0.84

Figure 4: Total intracranial volume, and specifically thalamic volume, is lower in HIV+ youth (but not controls) with cognitive impairment, compared to those without.



Results/Discussion

- Demographics and clinical characteristics of this cohort are described in **Table 1.**
  - HIV+ and uninfected control youth are very well-matched in demographics, education, socio-economic status, premorbid cognitive function, HIV risk factors, and trauma history.
  - HIV+ youth had relatively well controlled HIV, with low prevalence of viremia, and robust CD4 nadir counts
- Cognitive Impairment:
  - 11/16 (69%) of HIV+ youth met HAND criteria[10]; 2/16 asymptomatic neurocognitive impairment (ANI), 9/16 with functional impairment (MND/HAD). Global and median deficit scores are shown in **Table 1, Figure 1.**
    - However, 8/17 (47%) of control youth also met HAND criteria: 2/17 ANI, 6/17 with functional impairment
  - *Is another factor driving cognitive impairment in this population? (ACES, HAM-D, education, average weekly alcohol use, and average weekly marijuana use were not associated with HAND)*
- Neuroimaging analysis
  - We found 4% lower thalamus and 7% lower caudate volumes in HIV+ youth compared to well-matched controls (**Figure 2**).
    - No significant difference in total intracranial volume between groups, *supporting selective vulnerability of thalamus, caudate*.
    - Volume loss not homogenous across structures: HIV+ youth may have more volume loss than controls proximal to CSF interface in both caudate and thalamus (**Figure 3**), *raising the possibility of a specific CSF toxicity gradient.*
    - Trauma history (ACES), depressive symptoms (CES-D), education, average weekly alcohol use, and average weekly marijuana use did *not* associate with caudate volume (**Table 2**).
  - HIV+ youth with cognitive impairment (GDS ≥ 0.5) had lower total intracranial and thalamic volumes than those without impairment
    - A similar relationship was *not* seen in control youth (**Figure 4**), *supporting a direct relationship between thalamic volume and cognitive impairment specific to HIV (rather than other SES determinants of health)*.

Conclusions and Future Directions

- We have established a robust method for quantification of structural and intra-regional analysis that differentiates HIV+ youth from well-matched community controls.
  - An intriguing new finding is the potential of a CSF-toxicity gradient. Further analysis of CSF for novel factors that may contribute to direct toxicity in this population is needed.
  - Future larger, longitudinal, cohorts of both youth and older adults will determine if patterns of volume loss are similar across ages, and will define whether changes in youth represent a static injury or a progressive degenerative process.
- HAND classification and cognitive impairment defined by deficit scores in this cohort did not clearly discriminate between HIV+ and HIV- youth in this cohort.
  - Age-specific HAND criteria may be necessary
  - Task-based functional MRI analyses are ongoing.