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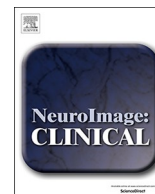
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## Mapping abnormal subcortical neurodevelopment in a cohort of Thai children with HIV



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### ABSTRACT

Alterations in subcortical brain structures have been reported in adults with HIV and, to a lesser extent, pediatric cohorts. The extent of longitudinal structural abnormalities in children with perinatal HIV infection (PaHIV) remains unclear. We modeled subcortical morphometry from whole brain structural magnetic resonance imaging (1.5 T) scans of 43 Thai children with PaHIV (baseline age =  $11.09 \pm 2.36$  years) and 50 HIV- children ( $11.26 \pm 2.80$  years) using volumetric and surface-based shape analyses. The PaHIV sample were randomized to initiate combination antiretroviral treatment (cART) when CD4 counts were 15–24% (immediate:  $n = 22$ ) or when  $CD4 < 15\%$  (deferred:  $n = 21$ ). Follow-up scans were acquired approximately 52 weeks after baseline. Volumetric and shape descriptors capturing local thickness and surface area dilation were defined for the bilateral accumbens, amygdala, putamen, pallidum, thalamus, caudate, and hippocampus. Regression models adjusting for clinical and demographic variables examined between and within group differences in morphometry associated with HIV. We assessed whether baseline CD4 count and cART status or timing associated with brain maturation within the PaHIV group. All models were adjusted for multiple comparisons using the false discovery rate. A pallidum subregion was significantly thinner in children with PaHIV. Regional thickness, surface area, and volume of the pallidum was associated with CD4 count in children with PaHIV. Longitudinal morphometry was not associated with HIV or cART status or timing, however, the trajectory of the left pallidum volume was positively associated with baseline CD4 count. Our findings corroborate reports in adult cohorts demonstrating a high predilection for HIV-mediated abnormalities in the basal ganglia, but suggest the effect of stable PaHIV infection on morphological aspects of brain development may be subtle.

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## 1. Introduction

Long-term survival and quality of life of children perinatally infected with HIV has improved dramatically with better access to combination antiretroviral therapy (cART). Pediatric HIV-related encephalopathy has decreased in the cART era (Patel et al., 2009; Raskino et al., 1999; Shanbhag et al., 2005), down to 1.6% from a prevalence of 76% prior to cART (Chiriboga et al., 2005; Cooper et al., 1998), greatly extending life expectancy. However, as the number of chronically-infected children living with HIV increases, there is a need to understand the impact of the infection on brain development. HIV is associated with cognitive and motor impairments in adults (Brew, 2004; Heaton et al., 1995; Sacktor et al., 2002) and children (Paul et al., 2018; Van Rie et al., 2008). In adults, these impairments are commonly associated with disruption to frontal subcortical circuitry, though recent studies indicate more diffuse effects in chronically infected individuals (Baker et al., 2017; George et al., 2009; Safriel et al., 2000).

Few studies have examined neuroimaging abnormalities in pediatric HIV. Work by Herting and colleagues (Herting et al., 2015) identified associations between HIV severity, peak viral RNA levels and nadir CD4%, and the functional connectivity of the default mode network (DMN). Interestingly, disease severity was related to both increased and decreased BOLD signal correlations both within and between DMN connectivity. These patterns of connectivity were also predictive of processing speed. The authors suggest that these findings may reflect a global reorganization of the DMN and underlie many of the cognitive dysfunctions found in youth with HIV.

Studies of microstructural brain integrity using diffusion tensor imaging reveal lower whole brain fractional anisotropy in HIV+ youths (Hoare et al., 2018; Uban et al., 2015), and increased mean and axial diffusivity with higher viral RNA load in plasma (Hoare et al., 2015). Macrostructural neuroimaging studies have yielded more equivocal results. Cohen et al. reported more severe white matter hyperintensities and lower gray and white matter volumes in HIV+ children age 8–18 compared to HIV-uninfected controls (Cohen et al., 2016). Hoare and colleagues reported decreased cerebral gray matter volumes, cortical surface area, and decreased gyrfication among 204 adolescence with paHIV between the ages of 9 to 11 years relative to 44 age-matched controls (Hoare et al., 2018). Sarma and colleagues reported lower volumes of the posterior corpus callosum and external capsule, but increased volumes of multiple cortical and subcortical gray matter regions (Sarma et al., 2014). Recent work by our group to clarify the discrepancies in gray matter volumes in pediatric HIV revealed larger volumes of the caudate, accumbens, and cortical gray matter in HIV+ children under age 12, with no differences in volumes among older children (Paul et al., 2018b).

Volumetric estimates of relatively large subcortical regions, however, are not sensitive to potentially subtle disease-related structural deformations in subsections or subfields of the structures that may better represent specific cell types. One means of modeling these more specific abnormalities is to use high-dimensional surface-based shape descriptors on the extracted subcortical region of interest. We have demonstrated that these shape features are highly sensitive to focal abnormalities when compared to volumetric measures in HIV+ older adults (Wade et al., 2015), as well as other patient populations (e.g., traumatic brain injury; (Tate et al., 2016; Tate et al., 2018) treatment-resistant depression (Wade et al., 2016; Wade et al., 2017).

To date, only one study has used shape analysis to characterize local subcortical deformations in youth with HIV. Lewis-de los Angeles and colleagues applied multiatlas FreeSurfer-initiated large-deformation diffeomorphic metric mapping (Khan et al., 2008) to identify subcortical shape deformations related to peak HIV viral load and nadir CD4% in PHACS, a cohort of 40 youth from the United States, all with perinatally acquired HIV (PaHIV). The group found deformations of the thalamus, caudate, pallidum, and putamen related to peak HIV RNA counts. Most deformations were inwards, although outward

deformations were also detected; these outward deformations, local volumetric expansion, of the medial and posterior thalamus were identified in association with higher nadir CD4%. Further, shape variations in the caudate and thalamus were associated with cognitive impairments (Lewis-de Los Angeles et al., 2016).

Nearly all of these previous studies were limited by their cross sectional designs, and many did not compare the HIV+ individuals to matched controls. In this study we investigated whether HIV status associated with cross sectional or longitudinal structural deformations in seven subcortical brain regions in a relatively homogeneous sample of 43 youth with HIV compared to 50 uninfected controls, all from three scanning sites across Thailand. Participants (age 6 to 16) were enrolled in a longitudinal study to examine outcomes associated with early versus deferred initiation of cART (ClinicalTrials.gov, number NCT00234091; (Puthanakit et al., 2012)). Both adult and adolescent HIV literature suggest a disproportionate effect of HIV status on subcortical brain structures (Fennema-Notestine et al., 2013; Jernigan et al., 2011), particularly the basal ganglia (Ances et al., 2012; Li et al., 2018; Wade et al., 2015). Given this and the need to restrict the number of statistical comparisons, we focused our analyses on prominent subcortical regions of interest. We hypothesized that children with HIV would exhibit significant deformations in select brain regions, with reduced local and global volumetric distortions. Within the HIV+ subset, we further evaluated the effect of current CD4 count, and cART treatment status or timing (early versus deferred initiation), on subcortical morphometry; we hypothesized that higher CD4 count would show patterns more similar to HIV- controls while cART treatment status would not show any effects.

## 2. Methods

### 2.1. Participants

The sample included 43 HIV+ (baseline age =  $11.09 \pm 2.36$ ; 20 female; 32 on cART; 21 deferred cART) and 50 HIV- (baseline age =  $11.26 \pm 2.80$ ; 29 female) Thai participants enrolled in the Pediatric Randomized Early versus Deferred Initiation in Cambodia and Thailand (PREDICT) clinical trial (ClinicalTrials.gov, number NCT00234091; (Puthanakit et al., 2013; Puthanakit et al., 2012)). Baseline demographic and clinical characteristics of the groups are provided in Table 1. Enrollment into the PREDICT trial occurred between 2005 and 2007, resulting in 150 children randomized to the immediate arm, 150 randomized to the deferred arm. Two control samples were recruited, including 164 healthy unexposed uninfected (HUU) and 155 HIV-exposed but uninfected children (HEU) (Puthanakit et al., 2013). A neuro-focused substudy was initiated after the start of the main PREDICT trial, which included neuroimaging and neuropsychological assessment. This study includes HIV+, HEU, and HUU children who completed the neurosubstudy. For this imaging analysis, all participants met the following inclusion criteria: (1) age < 18 years, (2) able to tolerate MRI, and (3) written informed consent signed by a caregiver and assent for participants 6 to 17 years of age. Exclusion criteria included prior or current brain infection, neurological or psychiatric disorder, any congenital abnormality or head injury with a loss of consciousness. The Institutional Review Boards (IRBs) of each study site approved the study.

### 2.2. Image acquisition

Participants underwent repeat structural magnetic resonance imaging (MRI) with an average of 52 weeks between baseline and follow-up scans (median = 52.7 weeks; range = 39.2 to 116.7). Whole brain structural T1-weighted MRI was performed on GE 1.5 T scanners at all study sites using the following protocol: axial plane, 3D SPGR images with a minimum TE at full echo, TR = 11.2ms, slice thickness = 1.0 mm, isotropic voxel size;  $256 \times 256$  imaging matrix. The

**Table 1**  
Demographic and clinical characteristics.

	HIV+ (n = 43)	HIV- (n = 50)
Age, mean (sd), y	11.09 (2.36)	11.26 (2.80)
Sex, M/F	23/20	29/21
cART status, Y/N	32/11	–
Age of cART initiation, mean (sd), y <sup>a</sup>	9.39 (3.23)	–
Log Viral RNA count, mean (sd), copies/ml	9.85 (11.16)	–
Detectable/undetectable vRNA, (%) <sup>b</sup>	25/75	–
CD4 count, mean (sd), cells/mL <sup>c</sup>	728 (323)	954 (299)
HEU/HUU	–	25/25
Site, Chula/CM/KKU	15/25/3	20/29/0
Income, above average/average/below average	1/14/20	8/24/18
Education, high school or greater/up to elementary school	18/25	23/26
Days to follow-up <sup>c</sup>	472.69 (140.84)	364.44 (42.97)

<sup>a</sup> Based on the date that a participant received the first drug in the cART cocktail.

<sup>b</sup> Undetectable vRNA levels are < 50 copies per mL.

<sup>c</sup> Significant difference.

number of slices acquired were between 130 and 170, and varied per scan to ensure full head coverage. Quality assurance of the MRI acquisitions was performed throughout the study using a human phantom to ensure consistent scaling. Motion was assessed in real-time by the technician. The scan was repeated for any participant for whom motion artifacts were detected. All participants with longitudinal MRIs used for this analysis had at least one scan without detectable motion at each time point. Therefore, motion was not a significant issue at the image processing stage, and no data points were excluded after the data collection was completed. Two of the authors (N.J. and B.W.) reviewed all subject's FLAIR images to screen for white matter hyperintensities (WMH) that might compromise regional FreeSurfer segmentations. No concerning WMHs were identified in scans of participants that had originally passed quality control, thus there was no need to exclude more data on this basis.

### 2.3. Morphological descriptors

FreeSurfer version 5.3 (Fischl et al., 2002) was used to remove non-brain tissue, normalize intensities, and conducted semiautomated volumetric parcellation using probabilistic information from manually labeled training sets. FreeSurfer's default cross-sectional workflow was applied to each scan. Seven subcortical brain regions of interest (ROI) were selected: the thalamus, putamen, pallidum, amygdala, accumbens, caudate, and hippocampus. Segmentations were completed for each hemisphere with visual quality inspection completed using ENIGMA protocols: <http://enigma.usc.edu/protocols/imaging-protocols/> to ensure their quality.

To define shape descriptors on the subcortical surfaces, a 3D coordinate mesh was applied to the outer surface of each ROI. The parameterization of each surface was obtained using the medial "Demons" framework detailed in (Gutman et al., 2015; Gutman et al., 2012). Briefly, each surface was conformally mapped to the spherical domain and rigidly rotated to a probabilistic atlas. Each segmentation was warped to a spherical template using Spherical Demons (Gutman et al., 2013) on the basis of curvature to define the local thickness of the surface with respect to a skeletonization or the surface "medial core." The medial core and surface-based curvature were mapped to each surface to render two measures at each point along the surface: (1) the radial distance (RD), a proxy for the local thickness, and (2) the log of the Jacobian determinant (JD) which indicates regional surface area expansion or contraction. For example, if the anterior hippocampus were significantly thinner in a group of elderly patients with Alzheimer's disease compared to age-matched controls, the RD value would be

smaller in the anterior hippocampus of the Alzheimer's patients. If instead the healthy cohort hippocampi did not differ from the Alzheimer's group on the basis of local thickness but was relatively elongated, the log-JD would be positive for the healthy group but negative for the Alzheimer's group, on average. We note that a shorter, yet thicker region, may not show a difference in volume, yet the shape characteristics defined here would help identify these trends. A total of 27,120 vertices were assessed across the fourteen (seven left and right) selected ROIs.

### 2.4. Statistical methods

Fixed effects multivariate linear regression analyses were used to model associations between the subcortical shape features (RD and JD) or volume and HIV-related factors at baseline and over time. HIV status represented the main effect of interest tested across all vertices (modeled categorically). We covaried for age, sex, total estimated intracranial volume, measures of socioeconomic status, including education level of the caregiver (modeled categorically: greater than elementary school level or not) and their income level (modeled categorically: average, above average, or below average). As scans were collected across three institutions across Thailand, we also adjusted for scan site (modeled categorically; 3 sites) in all models. Within the HIV + group, we separately assessed the effects of baseline CD4 t-cell count (modeled continuously), cART status (modeled categorically), and cART timing (modeled categorically as deferred versus immediate initiation) keeping the same covariates as before.

Longitudinal models assessed the relationship between HIV status and the change in the morphometry over time. Difference scores for both RD and JD were defined as  $\text{morphometry}_{\text{follow-up}} - \text{morphometry}_{\text{baseline}}$ , and longitudinal models included an additional covariate to model the time between the scans (in days).

Some variables had missing information: caregiver income level ( $N = 8$ ) and education level ( $N = 1$ ). We therefore ran two models. In the first, the subjects with missing data were not included in the models, and the second, the missing values for these data were imputed according to the overall mode of the sample: for patient income this was *average* and *elementary school or below* for education.

All models were adjusted for multiple comparisons across vertices for shape measures and across structures for volume measures using the standard false discovery rate (FDR) method with a false-positive rate of 5% ( $q = 0.05$ ) (Benjamini and Hochberg, 1995). FDR adjustments were applied within the family of all tests performed on a single surface correcting for separate tests within each surface. We further required that a minimum of three adjacent vertices show a significant association with the main effect, after adjustment for vertex wise multiple comparisons, to be considered a viable association; this further reduces the likelihood of false positives. Volumetric models were adjusted using FDR applied to the whole set of ROIs tested.

## 3. Results

### 3.1. Demographics

HIV+ and HIV- participants did not differ significantly by age (Welch  $t = -0.31$ ,  $df = 90.96$ ,  $p = .75$ ) or sex ( $\chi^2 = 0.80$ ,  $df = 1$ ,  $p = .36$ ). Baseline CD4 counts differed significantly by HIV status (mean HIV- = 954 per  $\mu\text{L}$ ,  $sd = 299.81$ ; mean HIV+ = 727 per  $\mu\text{L}$ ,  $sd = 325.29$ ; Welch  $t = -3.46$ ,  $df = 86.30$ ,  $p = .001$ ). Days to follow-up differed significantly between groups (Welch  $t = 4.84$ ,  $df = 48.85$ ,  $p < .0001$ ) with the average days to follow-up for HIV- being 364.44 ( $sd = 42.97$ ) and HIV+ being 472.69 ( $sd = 140.84$ ). There were no significant differences in age, sex or days to follow-up between cART-positive (cART+) and cART-negative (cART-) HIV+ participants. Baseline CD4 counts differed significantly by cART status (mean cART+ = 853.53 per  $\mu\text{L}$ ,  $sd = 270.80$ , mean cART- = 362.54 per  $\mu\text{L}$ ,  $sd = 140.49$ ; Welch  $t = 7.68$ ,  $df = 33.97$ ,  $p < .00001$ ).



### 3.2. HIV status

The thickness (RD) of the right medial inferior pallidum was significantly lower in the HIV+ group, relative to controls by approximately 4%. The area of this shape deformation covered 0.06% of the right pallidum surface (8 adjacent vertices; mean  $t$ -value =  $-4.002$ ; mean  $p$ -value  $< .001$ ) is illustrated in Fig. 1. The extent of this significant association was only moderately increased when income was not included as a covariate (see Supplementary Fig. 1) but was eliminated when subjects with missing income values were excluded (i.e., when we did not impute their values). No volumetric associations with HIV status were found at baseline. No longitudinal differences in shape or volume measures were associated with HIV status.

To confirm that shape and volume measures associated with development, we evaluated the effect of age in the same regression models in which HIV status was the main effect. We observed widespread associations between RD, JD, and volume measures with age across all subcortical regions at baseline; only a minority of regions exhibited longitudinal volumetric associations with age.

Similarly, we evaluated shape and volume associations with income and education levels to determine if these socioeconomic measures confer a larger effect on morphometry than HIV status. At baseline, no associations were found with education level, however, the volume of the bilateral putamen and JD of the right putamen ( $\sim 8\%$  of the total surface) was significantly reduced in subjects with an average income relative to those with above average income. An important caveat, though, is that there were only  $n = 9$  participants in the above-average-income category. No longitudinal associations with socioeconomic or demographic measures were observed longitudinally.

### 3.3. Baseline CD4 count and treatment status within HIV+ adolescents

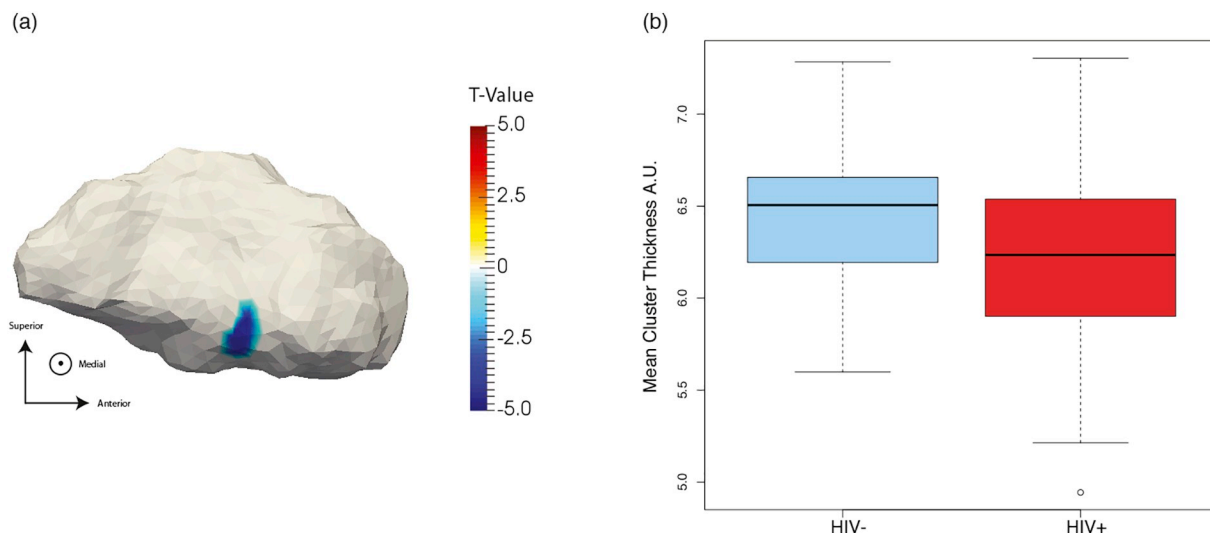
Baseline CD4 count was significantly associated with RD across 43% of the total surface of the left pallidum (mean  $t$ -value =  $-3.0$ ; mean  $p$ -value  $< .01$ ); see Fig. 2 (a-b). Similarly, baseline CD4 count was significantly associated with JD across 34% of the surface of the left pallidum (mean  $t$ -value =  $-3.0$ ; mean  $p$ -value  $< .01$ ); see Fig. 2 (c-d). The distribution of significant associations with CD4 count were similar when we did not covary for income level (see Supplementary Fig. 2). When the eight PaHIV participants with missing covariate information (specifically missing family income) were excluded the extent of the significant association with CD4 count was greatly reduced in the left pallidum and additional regional associations in the right caudate and

bilateral amygdala were identified (see Supplementary Fig. 3). The total volume of the left pallidum was also significantly and negatively associated with baseline CD4 count ( $t = -3.42$ ;  $p < .05$ ;  $b = -0.42$ ); see Fig. 3(a). The significance of this association remained when income was not included as a covariate but did not survive when participants with missing income data were excluded. All significant associations were such that participants with higher CD4 counts had smaller RD, JD, and volume measures, on average. Baseline CD4 count was significantly associated with the trajectory of the left pallidal volume ( $t = 3.32$ ;  $p < .05$ ;  $b = 0.25$ ) but not shape; children with higher CD4 counts had increased rates of left pallidum volume growth compared to those with lower CD4 counts (see Fig. 3(b)). This significant longitudinal association, however, did not survive multiple comparisons correction when four potential outliers in the volumetric range flagged by the interquartile range rule were excluded ( $p > .1$ ). As hypothesized, neither cART status nor cART timing were significantly associated with baseline or longitudinal shape or volume among the participants with HIV.

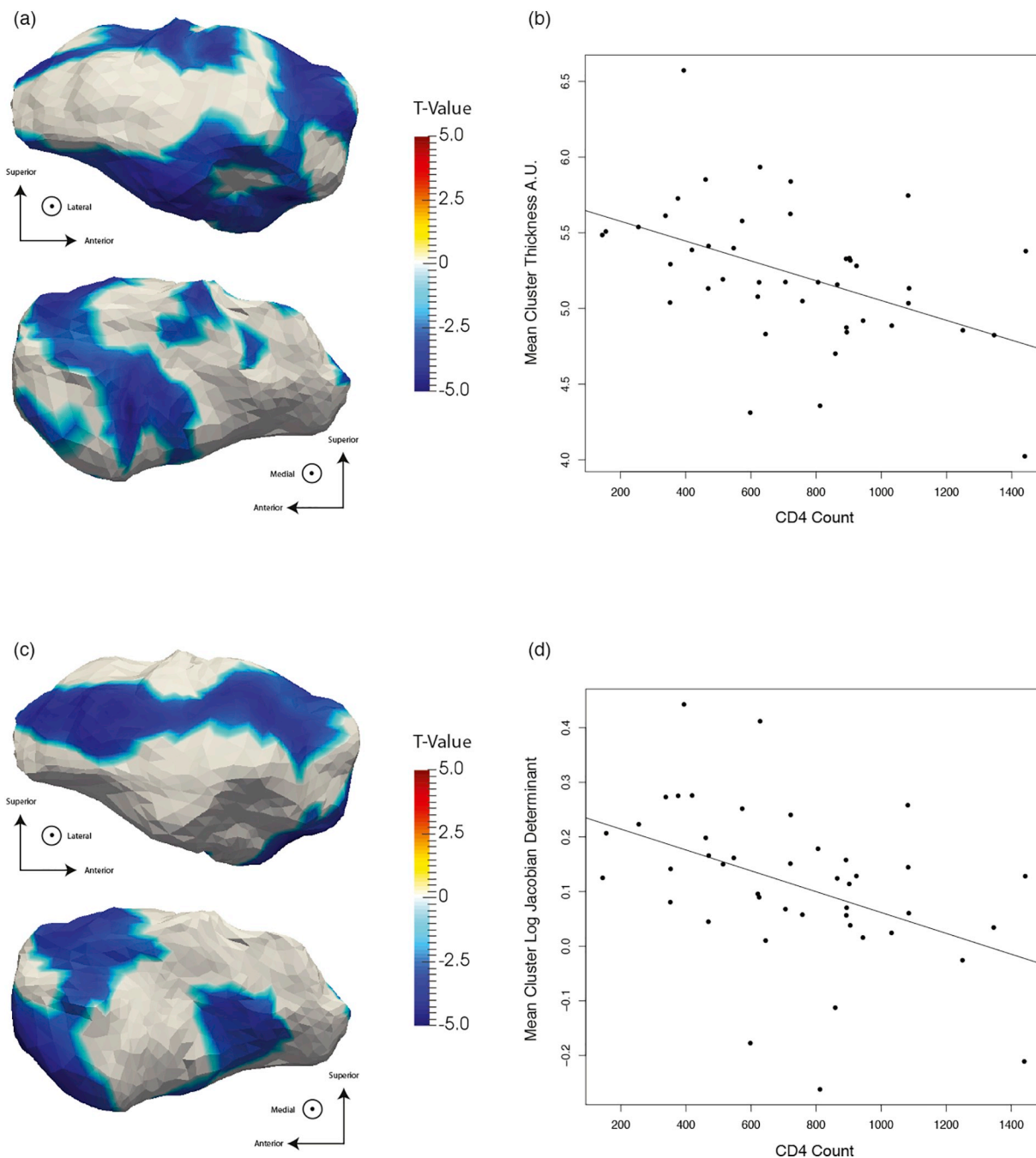
## 4. Discussion

In this study we observed a strong association between CD4 t-cell count and regional morphometry of the left pallidum among adolescence with HIV. Specifically, those with higher CD4 counts had reduced thickness and surface area of pallidal subregions and total pallidal volume. Nevertheless, longitudinally, the left pallidum total volume increased significantly more among children with higher baseline CD4 counts. We further observed that adolescence with HIV had only minimal morphological differences compared to uninfected controls at baseline; income level was seemingly more associated with subcortical shape and volume than HIV status. Nevertheless, a medial inferior region of the right pallidum was thinner in adolescence with HIV compared to controls. Longitudinal volumetric differences were associated with baseline CD4 count; however, no longitudinal shape or volume differences were associated with HIV or cART status.

The basal ganglia has been shown to be highly affected in HIV (Aylward et al., 1993; Berger and Arendt, 2000; Berger and Nath, 1997; Wright et al., 2016). The predilection for the basal ganglia may be mediated through a multi-deterministic model including weak tight junctions between astrocytic feet comprising the blood brain barrier, high concentration of CCR5 chemokine receptors, and susceptibility to oxidative stress. Previous work by our group showed that the pallidum's volume is significantly reduced in elderly patients with HIV.



**Fig. 1.** Subcortical shape differences in the right pallidum between HIV+ and HIV- participants. (a) T-value map highlighting region of significantly different local thickness (RD value) associated with HIV status. (b) Boxplots of average local thickness in vertices identified as significantly different in (a).



**Fig. 2.** Left pallidum shape (RD top and JD bottom) associations with CD4 count within HIV+ participants. T-value maps highlighting clusters of vertices where shape is significantly associated with CD4 count; all were inversely associated (a & c). Figures b & d are scatterplots showing the average RD or JD values within significant regions plotted against participant CD4 count.

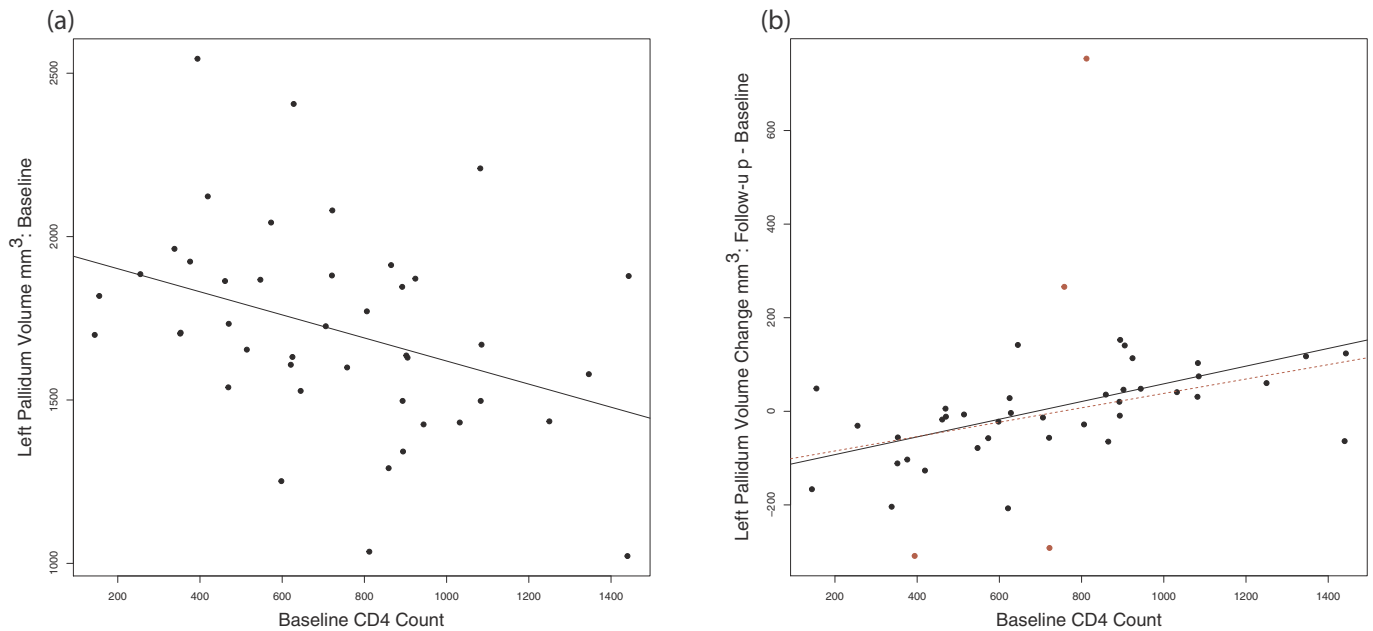
Interestingly, this same study identified a trend-level increase in the local volume of the anterior right pallidum associated with extended time since diagnosis (Wade et al., 2015). Lewis-de Los Angeles et al. also observed shape variations, both local volumetric dilations and reductions, of the pallidum and putamen associated with HIV severity (as captured by peak HIV RNA load) (Lewis-de Los Angeles et al., 2016). Our finding suggests that on average, adolescents with higher baseline CD4 counts have lower regional thickness, surface area, and total volume.

While in most cases, larger or thicker neuroimaging derived subcortical regions are considered to be associated with healthier brains, this is not always the case, particularly for the pallidum. For example, Turner and colleagues reported significantly larger pallidum volumes in

people with autism spectrum disorder (ASD) based on a sample of 472 ASD and 538 non-ASD controls between the ages of 6–64 years (Turner et al., 2016). Jørgensen et al. also reported an increased volume of the pallidum among 82 patients with long-term treated schizophrenia relative to 106 healthy controls (Jørgensen et al., 2016). Enlarged pallidum volumes in schizophrenia was also reported in a much larger study by van Erp and the ENIGMA consortium who reported an increased pallidum volume in a meta-analysis of 2028 patients with schizophrenia and 2540 controls (van Erp et al., 2016).

More directly related to our current study, Randall et al. investigated abnormalities in subcortical gray matter volumes in 43 HIV+ and 18 HIV- 5-year old Xhosa children who were initiated to ART before 18 months of age; 27 initiated ART before 12 weeks of age and





**Fig. 3.** Scatterplots highlighting the significant associations between baseline CD4 counts and (a) baseline left pallidum volume and (b) the change in left pallidum volume between baseline and follow-up time points. In b, red points indicate four subjects that are potentially outliers in terms of volumetric change as flagged by the interquartile range rule. The red dashed regression line is fit to the set of subjects excluding the potential outliers.

16 initiated after 12 weeks. The group reported that HIV+ children had larger left pallidum volumes compared to the uninfected group and that this difference was largely driven by children initiated to ART after 12 weeks of age (Randall et al., 2017). The authors suggest that larger differences in the later-initiated group is evidence neuroprotective effects of earlier treatment. Our analysis of cART timing and status, however, did not identify significant associations with brain morphometry. This is possibly due to two factors: The number of children in this sample who did not undergo cART was very small thus limiting the power of between-group analyses. Additionally, children were selected for the parent study due to ability to survive without cART at the time of randomization. Thus, survivor tendencies may mitigate our ability to detect direct associations with cART and its benefits.

The absence of cART-related findings in this cohort squared with our expectations for several reasons. Children in the parent study were treatment-naïve at the time of enrollment. The participants were then randomly assigned to begin cART when CD4 < 15% or when CD4 < 25% deferred or immediate treatment arms. Thus, only some of the original deferred group would not be on cART at baseline. Further, as only 11 children were untreated at baseline, we anticipated that this sample was underpowered to resolve treatment effects.

Though speculative, it is possible that the observed inverse correlation between CD4 count and left pallidal volume reflects ongoing disease mechanisms among individuals with low CD4 cell count; but, further studies directly assessing markers of inflammation are needed to test this hypothesis. Further, higher baseline CD4 counts were significantly associated with increased subsequent growth of the left pallidum's total volume which suggests that pallidal growth is increased in healthier adolescence.

HIV-associated cognitive impairment is an important topic of investigation and has been widely reported in a number of previous studies (Brew, 2004; Sacktor et al., 2002; Van Rie et al., 2008). We did not explore associations between cognition and brain morphometry in this study, however, as a prior study of this same cohort described cognitive abnormalities in paHIV and reported minimal disease-related cognitive changes (Paul et al., 2018). As such, the present study was

conducted to investigate brain integrity longitudinally in paHIV using an innovative and sensitive analysis of parenchymal morphology.

Several notable limitations should be considered in interpreting these findings. First, the one-year time frame between baseline and follow-up scans may not have been sufficient to observe important changes. The average baseline age of our participants was 11 years and ranged from 6 to 16 across diagnostic groups, an age span characterized by complex patterns of age and sex-dependent rates of gray matter pruning and myelination (Giedd, 2004). Given this, a wider time frame and future follow-up imaging sessions would be beneficial. However, numerous baseline and longitudinal abnormalities among the HIV+ cohort were identified. We additionally note that the time to follow-up was significantly longer in the HIV+ cohort. While this cannot be completely corrected, we included time to follow-up as a covariate in our longitudinal models. As discussed previously, the original sample included three time points, however, the HIV+ cohort was a year older at baseline relative to the control group and it is possible that the use of different baseline time points across the two groups introduced a systematic bias in our models. Another limitation for this study was that certain data points, primarily for income level, required imputation. While this is an inherent limitation, we observed only minor differences in the distribution of significant associations between models that included or excluded income levels (see Supplementary Figures).

In conclusion, we observed shape abnormalities among HIV+ children at first scan, which attenuated in magnitude over the course of 12 months as longitudinal subcortical abnormalities were non-significant. The most robust HIV-related effects were instead shape and volumetric associations with CD4 cell count within the pallidum of paHIV children. Although more work needs to be done to disentangle potential effects of neuroinflammatory processes, this approach has not previously been applied to identify abnormalities in longitudinal imaging profiles of children with paHIV. Taken together, our findings suggest that the effects of treated HIV on the morphometry of subcortical structures in adolescence is somewhat minor.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.nicl.2019.101810>.

## Conflict of interest

JA has received honorarium for advisory meetings participation from Merck, ViiV Healthcare and Tetralogic. PMT and NJ have research related grant support from BioGen Inc., unrelated to the contents of this manuscript. Other authors have no disclosures related to the study.

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