White Matter Abnormalities in Perinatally HIV-Infected Youths: A Diffusion Tensor Imaging Study

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Target audience: Basic and Clinical Researchers working on Neuro-Imaging of HIV infections, and cerebral metabolism in HIV-infected youths.

Purpose/Introduction: Due to effective antiretroviral therapies [1], many perinatally HIV-infected youths have now survived to adolescence and adulthood. Since these patients acquired HIV at a time of relative immune compromise (in utero and at birth), signs of neurocognitive compromise are common [2]. While the adverse effects of HIV on neurological function have been well-established, there have only been a few MRI studies that have addressed the affect of HIV on white matter (WM) integrity [3, 4, 5] and these studies are on adult patients. The affect of HIV on WM integrity of perinatally HIV-infected youths is yet to be explored. In this study we examined four diffusion tensor imaging (DTI) metrics including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), across a group of perinatally HIV-infected youths and a control group, matched for age. The primary aim of the current study was to compare FA, MD, AD, and RD changes in different brain regions of perinatally HIV-infected youths compared to healthy controls using an automated atlas based analysis for regional parcellation that uses Large Deformation Diffeomorphic Metric Mapping (LDDMM) for non-linear registration.

Materials and Methods: We investigated six HIV infected patients (age 15.5y± 2.1 years) and five healthy controls (age 15.2y± 1.6 years) who underwent MRI/MRS using a 12 channel head phased array 'receive' coil. All subjects gave informed consent according to an institutionally approved research protocol. A Siemens 3T Trio-Tim MRI scanner (Siemens Medical Solution, Erlangen, Germany) was used and DTI was performed using a single-shot multi-section spin-echo echo-planar pulse sequence [repetition time (TR) = 10,000 ms; echo-time (TE) = 90 ms; average = 4] in the axial plane, with a 130 x 130 matrix size, 256 x 256 mm^2 field of view (FOV), 2.0 mm slice thickness, 75 slices. For each slice, diffusion gradients were applied along 12 independent orientations with b =1000 sec/mm^2 after the acquisition of b = 0 sec/mm^2 (b0) images.

DtiStudio [6] was used to calculate FA and MD. Before the normalization procedure, the skull was stripped using the b0 images and a skull-strip tool in RoiEditor software [7] using a modified version of the active contour method described by Chan and Vese [8]. A representation of the subsequent normalization process, performed using DiffeoMap [9]. The images were first normalized to the JHU-MNI-SS template using a 12-parameter affine transformation of AIR. For the non-linear transformation, dual-contrast Large Deformation Diffeomorphic Metric Mapping (LDDMM) [10] was employed. The atlas-based analysis was performed using a WM parcellation map (WMPM) [11]. Briefly, the brain was parcellated into 130 regions based on anatomical labeling, including both the gray and WM. Because of the reciprocal nature of the LDDMM, the transformation results can be used to warp the WMPM to the original MRI data, thus automatically segmenting each brain into the 130 subregions. These initial segmentation results (130 regions) were further segmented to separate the cortex and the associated peripheral WM, using the FA threshold, FA≥0.25 (Fig. 1). Statistical analysis was done using analysis of covariance (ANCOVA) model with age and gender as covariate. Significance was determined with a P value of 0.05.

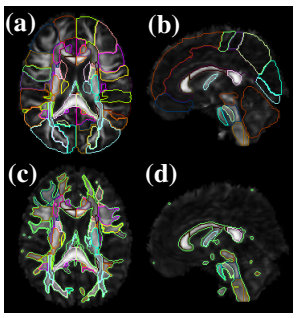

Fig. 1: (a) & (b) Axial and sagittal view of JHU-MNI-SS-WMPM-Type II atlas superimposed on a 13 years old HIV infected subject's FA map. (c) & (d) Corresponding segmented image after applying FA threshold of 0.25.

Results: We found significant regional group differences in FA (Table 1) and AD (Table 2). Compared with healthy-control subjects, the HIV-infected group exhibited statistically significant decreased FA in the left: inferior occipital gyrus, cingulum, body of corpus callosum, thalamus, and right: fornix/Stria terminalis, inferior frontal gyrus, anterior limb of internal capsule. We observed a trend for increased MD in the HIV infected youth compared to the healthy control with statistically significant elevation in the right entorhinal area (0.916±0.08 vs 0.782±0.06 ($\times 10^{-3}$ mm^2/s); p=0.028) only.

Regions	Healthy Controls	HIV-infected Youths	p-value
Lingual gyrus left	0.360±0.015	0.342±0.007	0.057
Inferior occipital gyrus left	0.372±0.004	0.346±0.016	**0.008**
Cingulum (hippocampus) left	0.413±0.012	0.391±0.015	**0.022**
Genu of corpus callosum left	0.641±0.018	0.625±0.011	0.132
Body of corpus callosum left	0.585±0.008	0.568±0.015	**0.044**
Thalamus left	0.370±0.008	0.359±0.007	**0.039**
Fornix (cres) / Stria terminalis right	0.468±0.010	0.446±0.020	**0.043**
Inferior frontal gyrus right	0.405±0.011	0.388±0.013	**0.039**
Anterior limb of internal capsule right	0.545±0.012	0.526±0.014	**0.043**
Superior cerebellar peduncle right	0.537±0.009	0.504±0.033	0.060

Table 1: Summary of FA (mean±SD) value changes in HIV infected youths compared to healthy controls. Regions significant at p <0.05 are highlighted in bold.

Changes in AD are shown in Table 2. We found statistically significant increases in AD in left limb of internal posterior capsule, right entorhinal area and external capsule. We also found an increasing trend for RD in the HIV infected youth compared to the healthy control group in several regions of the brain including right entorhinal area and inferior frontal gyrus, left putamen and posterior corona radiata.

Regions	Healthy Controls	HIV-infected youths	p-value
Posterior limb of internal capsule left	1.20±0.02	1.22±0.02	**0.038**
Fusiform gyrus right	0.93±0.02	0.97±0.05	0.074
Parahippocampal gyrus right	0.99±0.05	1.05±0.04	0.052
Entorhinal area right	1.06±0.09	1.20±0.11	**0.036**
External capsule right	0.99±0.01	1.02±0.03	**0.035**

Table 2: Regional AD (mean±SD) value ($\times 10^{-3}$ mm^2/s) changes in HIV infected youth compared to healthy control. Regions significant at p <0.05 are highlighted in bold.

Discussion and Conclusion: This study provides evidence that white-matter integrity is compromised in perinatally HIV infected youths. Our results showed widespread brain regions with decrease of FA and elevation of AD values in perinatally HIV infected youths relative to healthy controls. We also observed a trend of increased MD and RD values in this group of HIV subjects. These findings are consistent with previous studies using adult HIV patients [3,4, 5] suggesting that HIV infection affects neuronal integrity. The decrease in WM integrity is best seen in the decrease in FA representing loss of parallel fibers or fiber coherence. An increase in AD values represents reduced axonal density or caliber in those regions. Also, increased MD typically signifies general tissue breakdown and increased RD represents loss of myelin integrity. Further studies will be required to validate and elaborate these findings on a large cohort of subjects; however, this study advances our knowledge of neurological impact of HIV in perinatally infected youths. Assessment of the neurological function of these youths as they continue to survive for many years is important, since sensitive early detection of neurologic compromise might result in treatment modifications that could ultimately improve their brain health and function.

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