Patterns of CNS Injury in HIV Infection: a DTI Tract-Based Spatial Statistics Study

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INTRODUCTION: It is well established that HIV infection is associated with injury to the central nervous system (CNS) that can lead to cognitive impairment, including dementia. Autopsy studies have shown involvement of grey matter (especially subcortical areas) and white matter structures in the disease process. Although the introduction of combined antiretroviral therapy (cART) has significantly improved survival, recent studies including work from the HIV Neuroimaging Consortium (HIVNC) have shown evidence of persistent and progressive brain injury as measured by magnetic resonance spectroscopy and morphometry in the setting of stable HIV disease [1]. We have presented preliminary results [2] using Tract-Based Spatial Statistics [3] to investigate changes in white matter structures across the entire brain in HIV-infected subjects on cART. We now report and extend analysis that also includes the correlation between tensor derived parameters and neuropsychological test scores to further investigate the structural-functional relationship of HIV-associated CNS injury.

METHODS: Participants included 50 HIV infected individuals and 13 age-matched normal controls. AIDS Dementia Complex (ADC) score was used to further categorize the HIV infected individuals into two groups: HIV+ neuroasymptomatic (HIV+NA: ADC=0 or 0.5; N=42 subjects) and HIV+ cognitively impaired (HIV+CI: ADC$\geq$ 1; N=8 subjects). For each HIV+ subject, a set of clinical scores was also obtained, including seven neuropsychological testing scores (speed of information processing, verbal fluency, working memory, verbal memory, learning, executive function and motor speed) and the duration of HIV infection. All DTI acquisitions were performed on a GE 1.5T scanner using a single shot EPI-DTI sequence with TR/TE=9000/85ms, 2x2x5mm voxel, 21 diffusion gradient directions with b = 1000s/mm^2. Image processing steps and statistical analyses were performed using Tract-Based Spatial Statistics (TBSS) toolbox within FSL package (FMRIB, Oxford, UK). Three different statistical analyses were performed. (1). Detection of DTI changes: Three group statistical comparisons on FA and MD maps were performed between HIV+CI and controls (8 vs. 13), HIV+NA and controls (42 vs. 13), HIV+CI and NA (8 vs. 42). Changes of FA and MD within the white matter (WM) skeleton were characterized with permutation tests using the Randomize toolbox in FSL. (2). Predictive power of FA/MD for HIV+ clinical outcomes: For each white matter region where significant FA/MD changes were detected between two subject groups, the z-scores of FA/MD within the region were further analyzed by logistic regression with the study group type as the dependent variable. (3). Correlation between DTI and neuropsychological scores: For HIV+CI and HIV+NA groups, correlation analyses between FA/MD and each of abovementioned eight clinical scores were carried out within WM skeleton. All clinical scores are normalized with the demographical information, such as age and education, before correlation analysis using Randomize toolbox. For all TBSS-based analysis, correction for multiple comparisons was performed using the threshold-free cluster enhancement (TFCE) approach in FSL [4]. The John Hopkins White Matter Atlas [5] was used to identify WM structures with significant DTI changes or with significant correlation between DTI and clinical scores from the TBSS analysis.

RESULTS: TBSS analysis shows significantly decreased FA and increased MD values in multiple white matter structures as the disease progresses from neuroasymptomatic (ADC 0 and 0.5) to cognitive impairment (ADC $\geq$ 1) (**Tab. 1** & **Fig. 1**, top row). In the early stages of HIV-associated CNS injury (ADC 0 and 0.5), significantly increased MD values, compared to controls, were observed only within fiber bundles (**green** texts in **Tab. 1**) that are mainly associated or connected to the posterior areas of the frontal and the parietal lobes. These fiber tracts include the parietal section of callosal fibers (splenium of corpus callosum), projection fibers (bilateral superior and posterior corona radiata) and the parietal thalamic fibers (posterior thalamic radiation). On the other hand, no significant FA changes were detected between controls and the HIV+NA subjects. As CNS injury progresses (ADC$\geq$ 1) we observed both decreased FA and increased MD in the abovementioned fiber bundles. In addition, significantly decreased FA and increased MD values were also seen in fiber bundles connecting to the prefrontal lobes (**red** texts in **Tab. 1**), including the genu of the corpus callosum, the anterior corona radiata and limbic fibers (the bilateral cingulum tracts). Compared to controls while MD changes were present throughout the course of the disease, FA changes became significant only in cognitively impaired patients. In classifying HIV+CI vs. HIV+NA, both FA and MD in the body corpus callosum as well as MD values of bilateral anterior corona radiata were sensitive discriminators with the area under ROC curve (AUC) larger than 0.85. In addition, MD value of the splenium of the corpus callosum discriminated healthy controls from HIV+NA subjects (AUC>0.85). For HIV+ subject, significant correlations between both FA/MD and the verbal fluency test score were detected at multiple WM structures (green patches on images at bottom row of **Fig. 1**) including the body and the splenium of the corpus callosum, the superior and posterior corona radiate. For callosal fibers and projection fibers including the coronal radiata, significant changes of FA/MD in HIV+ subjects also significantly correlated with the duration of HIV infection.

CONCLUSIONS: Our results suggest that the combinations of DTI parameters such as FA and MD can differentiate control subjects from HIV+ infected subjects with and without cognitive impairment. The results also suggest a transition with more involvement of the frontal lobes in those subjects that develop cognitive impairment. The correlation with disease duration is consistent with this possibility. Among the different cognitive domains tested, verbal fluency had the highest correlation with DTI parameters. It is of interest that this cognitive domain is sub-served by neuronal circuitry that involves both the temporal and frontal lobes. As part of an ongoing project, we expect further validations of these results in future longitudinal analyses.

REFERENCES: [1] Cohen, R., et al, 2010, Journal of Neurovirology, (In press). [2] Zhu, T., et al., 2010, 16th annual meeting of OHBM, abstract 344; [3] Smith, S.M. et al., 2006. NeuroImage, vol.31, pp.1487-1505. [4] Smith, S.M., et al., 2009, Neuroimage, vol.44, no.1, pp.83-98. [5] Wakana, S., et al., 2003, Radiology, vol.230, pp.77-87.

Tab. 1. Regions with significantly decreased FA and increased MD with the progression of HIV+ from TBSS analysis

White matter structures	HIV+CI vs. Control		HIV+CI vs. HIV+NA		HIV+NA vs. Control	
	FA	MD	FA	MD	FA	MD
BCC	15.8	14.0	17.5	12.9	0	1.1
SCC	11.1	14.4	9.6	8.3	0	12.5
SCR (R)	3.5	12.3	3.6	11.6	0	2.7
SCR (L)	4.8	13.4	4.4	10.7	0	5.0
PCR (R)	12.7	19.4	9.2	13.9	0	14.0
PCR (L)	10.8	17.7	7.1	12.7	0	14.6
PTR (R)	3.2	11.8	0.5	0.5	0	12.2
PTR (L)	4.0	16.0	0.7	2.3	0	13.7
SLF (R)	1.2	11.9	0	3.5	0	9.6
SLF (L)	0.3	15.1	0.5	8.0	0	11.3
GCC	8.2	11.7	7.0	7.3	0	0
CIN (R)	1.4	4.7	3.7	3.3	0	0
CIN (L)	1.2	6.7	5.6	5.7	0	0
ACR (R)	2.2	18.7	11.6	15.4	0	0
ACR (L)	7.6	18.0	7.5	11.6	0	0
ALIC (R)	0	15.1	0	16.0	0	0
ALIC (L)	0	16.1	0	16.4	0	0
SFOF (R)	0	8.1	0	9.7	0	0
SFOF (L)	0	13.8	0	12.8	0	0

Note: Numbers listed in the table are the percent of voxels with significant altered FA/MD within each white matter structure from TBSS analysis (normalized by the total number of voxel within the corresponding structure of John Hopkins White Matter Atlas). Rectangular boxes indicate WM structures where the FA/MD are sensitive classifiers between groups with AUC>0.85 determined by logistic regression. Abbreviations: CI=cognitive impairment; NA=neuroasymptomatic. PTR=Posterior Thalamic Radiation; ALIC= Anterior Limb of Internal Capsule.
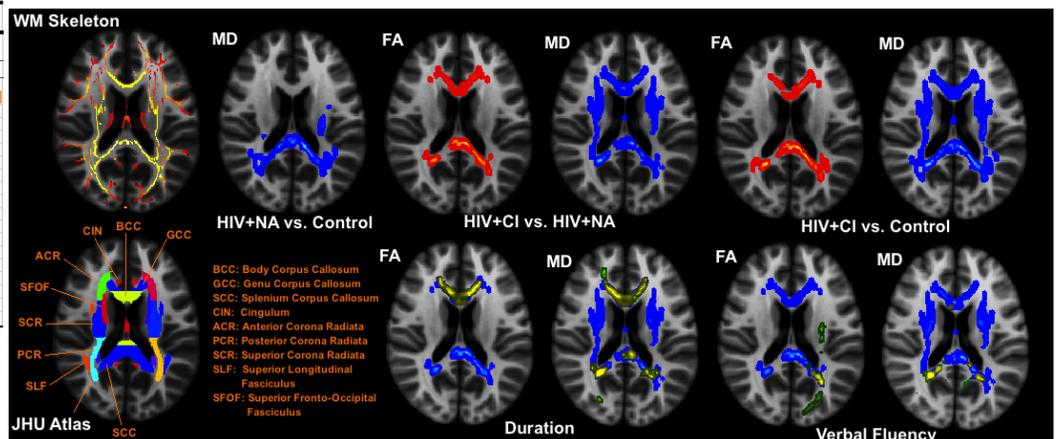

Fig 1. **(Top row)** TBSS results show significant decrease of FA and increase of MD with the pathological progression of HIV+ infections. Clusters with significantly decreased FA (red patches in the top row) and significantly increased MD (blue patches in the top row) in HIV+ are superimposed on the MNI152_T1 brain map (background). **(Bottom row):** For HIV+CI and HIV+NA, regions with significant correlation between DTI parameters and clinical scores (green patches) are superimposed on regions with significant decreased FA/increased MD in HIV+CI subjects (blue patches). The common, overlapped WM structures are highlighted with yellow color, including the genu and splenium corpus callosum, the anterior and posterior corona radiata.