DTI VBM Analysis of Pathological Progression in HIV Patients Underwent Associated Dementia

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Introduction: The pathogenetic mechanisms leading to Human Immunodeficiency Virus (HIV) associated dementia (HAD) have not been fully elucidated but histological studies in HIV subjects reveal that the predominant pathology affects diffusely the deep white matter (myelin pallor), while in subjects with HAD, in addition to diffuse white matter abnormalities, both subcortical structures such as the basal ganglia and cortex are involved [1]. Given the pathological changes affecting axons and dendrites described above, it is to be expected that water diffusion characteristics in brain tissues will be affected. These changes in water diffusion micro environment can be sensitively detected by diffusion tensor imaging (DTI). For each image voxel, tensor-derived metrics, such as Fractional Anisotropy (FA) and Mean Diffusivity (MD), provide quantitative measures of underlying tissue integrity and microstructural properties. Recently, DTI studies conducted in HIV-infected individuals have shown increased MD and decreased FA in the splenium and genu of the corpus callosum [2] and frontal white matter [3], based on statistical analysis of ROIs in these predefined regions. However, in the era of highly active antiretroviral therapy (HAART), the progression of the disease is slower than before HAART, subjects are living longer and potentially developing concomitant brain pathology associated with aging and cerebrovascular disease. Therefore, rather than investigating specific ROI, in this study, we used a voxel-based morphometry (VBM) approach to identify patterns of change in DTI parameters relative to the progression of HIV associated cognitive impairment. DTI was performed in three groups of subjects, HIV negative controls (HIV-), HIV positive individuals neurologically asymptomatic (HIV_NA) and HIV positive individuals with associated dementia (HAD).

Methods: *Subjects:* Three age- (46 +/- 14 yrs) and gender-matched groups were included in this study: 24 HIV- subjects, 7 HIV+ cognitively normal subjects, and 11 subjects with HAD. HIV subjects were on a stable antiretroviral regimen for at least 8 weeks prior to imaging. *Imaging:* All MR images were obtained on a Siemens 3T Trio system with an 8 channel head coil. DTI was performed according to the following sequence parameters: TR/TE=10100/100ms, isotropic 2x2x2 mm voxel size, matrix=128x128, iPAT (GRAPPA) acceleration factor =2, 24 diffusion gradient directions with b=1000 s/mm^2 and one average, b=0 images with 4 averages. High resolution (1x1x1mm) 3D MP-RAGE T_1W image and double-echo GRE images were acquired for the purpose of spatial normalization and field map, respectively. *Image Processing:* Custom-built software based on C++ and Matlab was used. Before the calculation of DTI parameters, additional correction steps for eddy-current and susceptibility artifacts were performed. *VBM analysis:* Custom-built software packages based on SPM tools were used for spatial normalization and VBM analysis. The processing pipeline followed the optimized VBM strategy [4]. A smoothing kernel 6x6x6mm (determined by possible size of HIV-related tissue damages) was applied to FA and MD image data before performing statistical analysis. In the first stage of statistical analyses, a one-way ANOVA of all three groups was performed, followed by a two-sample t-test for each combination of group pairing while significant differences were detected by ANOVA. Regions with significant differences in DTI parameters were used for interpretation of potential patterns of disease progression.

Results: ANOVA analyses revealed significant differences among groups but there were no significant voxels detected for any two-sample t-test between group pairs at p<0.05 level with FWE method for multiple comparison correction. Therefore, we further applied the combined small P value and cluster threshold to detect cluster-wise significant differences between groups (All the results reported here have corrected p<0.05 at cluster level, unless indicated otherwise). As shown in ***Figure 1***, a decrease in FA and an increase in MD is detected for the second (more pathological) vs. the first group in each pair. There was a decrease in FA and an increase in MD in several brain areas when HIV- were compared with HIV_NA or HAD. Decreased FA values (in cluster) were found in the Frontal and Temporal Lobe when the HAD group was compared to the HIV- group, as well as when HAD was compared to HIV_NA. Additional region with decreased FA was found at Left Sub-lobar area in HAD compared to HIV-. However, no region was detected with significantly different FA between HIV- and HIV_NA. MD increased bilaterally at the Limbic Lobes and at Right Temporal lobe in HAD compared to HIV_NA, while MD increase at more regions, such as Frontal Lobe bilaterally and Right Limbic Lobe, in HAD compared to HIV-. Detailed information of detected region is listed in ***Figure 1*** and ***Table 1***. Talairach coordinates [5] of typical regions are also included for reference.

	HIV- vs. HIV_NA		HIV- vs. HAD		HIV_NA vs. HAD	
FA	(50, -18,42)	Right Parietal Lobe (not significant)	(46,-48, -18)	Right Temporal Lobe	(8,52, -10)	Right Frontal Lobe
			(6,48,0)	Right Frontal Lobe	(52,-58, -10)	Right Temporal Lobe
			(-36, 14,2)	Left Sub-lobar		
MD	(-60, -56,28)	Left Temporal Lobe	(-14, 16, -26)	Left Frontal Lobe	(38,-26. -20)	Right Limbic Lobe
			(22,42, -20)	Right Frontal Lobe	(44,-28, -12)	Right Temporal Lobe
			(22,6, -26)	Right Limbic Lobe		

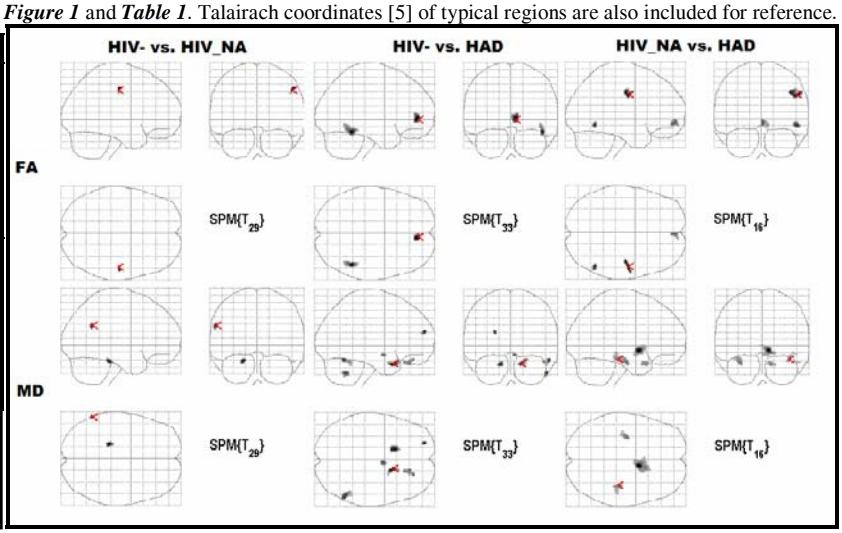

Figure 1 (Right): Regions that are significant different between groups at cluster-wise significant level (p<0.05), except FA between HIV- and HIV_NA which is not significant. "Hot spots" identify regions with decreased FA and increased MD for the second group; **Table 1 (Top)**: Examples of detected regions with Talairach Coordinates. Red for Gray matter while Blue for White matter.

Discussions: Results from our pilot study suggest a decrease in FA and increase in mean diffusivity, in the temporal lobe and frontal gray matter as well as subcortical white matter in HIV positive patients compared to normal controls. These findings are consistent with previously reported DTI-HIV studies in deep white matter regions [2,3] such as the corpus callosum. Tissue diffusion property changes in those regions may directly results from CNS involvement of HIV pathological processes, reflecting previously reported histological findings of leukoencephalopathy and poliodystrophy. Comparison of HIV- to HIV_NA, subjects yielded additional regions with increased mean diffusivity values. This finding is in agreement with previous MRS studies and hitopathological studies that have shown abnormalities even in subjects that are clinically asymptomatic. Furthermore, the differential pattern of DTI indices observed between HIV_NA and HAD may provide further insights in assessing progression of HIV-associated CNS injury in vivo. Instead of the traditional ROI-based method, VBM was used in this study in order to detect regions of HIV-associated pathology beyond previously reported regions. Although controversies exist, such as efficacy of related statistics power and potential mis-registration issues, VBM provides better time efficiency. Field map based susceptibility correction used in this study successfully removes the distortions in front lobes and make detections in these regions possible. On-going studies are correlating DTI metrics with clinical testing scores also collected in these patients. Further integration of DTI with other neuroimaging modalities, such as fMRI and perfusion imaging, may provide unique insights into the pathological mechanism of CNS involvement in HIV.

References: [1]. Gray F et.al. J Neuropath and Exp Neurology. 2003 May; 62(5): 429-40; [2]. Filippi CG et.al. AJNR 2001 Feb; 22(2): 277-83; [3]. Thurnher MM et.al. AJNR 2005 Oct; 26(9): 2275-81; [4]. Good CD et.al. NeuroImage 2001; 14: 21-36. [5]. Talairach Damon. *http://ric.uthscsa.edu/projects/talairachdaemon.html*

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