Early detection of subtle neurodegeneration in non-cognitively impaired HIV patients using TBSS and VBM

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TARGET AUDIENCE: This work is of interest to those interested in the early detection of neurodegeneration in HIV.

AIM: (1) To use quantitative MRI to study the early effects of subtle neurodegeneration in non-cognitively impaired patients with HIV. (2) To identify the effect of HAART on the development of neurodegeneration.

INTRODUCTION: The introduction of highly-active antiretroviral therapy (HAART) has increased the life expectancy and quality of life of patients with human immunodeficiency virus (HIV). In spite of this treatment, the incidence of HIV-associated neurocognitive disorders (HAND) has continued to rise [1]. This suggests that HAART may not provide neurocognitive protection or may even be detrimental to cognitive health. Although studies have shown the appearance of brain changes in HIV patients who are cognitively impaired [2-4], there have been no studies of those early in the development of HAND. Diffusion tensor imaging (DTI) has proven to be sensitive to subtle changes in the brain microstructure in a variety of white matter diseases and has been shown to identify early damage in advance of any neurological symptoms [5]. Voxel-based morphometry provides a measure of local volume changes in the brain. In this work, we use a combination of DTI, tract-based spatial statistics (TBSS) and VBM to identify subtle brain differences between patients who receive HAART, those that do not, and healthy volunteers.

METHODS: We recruited 36 participants (all males, age 30-50 years) in three groups: **Group A** (untreated HIV+, CD4=300-500; N=12), **Group B** (treated HIV+, CD4 < 40; N=12), **Group C** (healthy (HIV–) gay men; N=12). Subjects underwent a cognitive test to show they are not cognitively impaired. Scanning was conducted on a Siemens Avanto 1.5 T MR imager. Scanning parameters: DTI (EPI, TR=6400 ms, TE=111 ms, FOV=220 x 220 mm^2, matrix=128x128, slices=34, thickness=4 mm, 30 diffusion directions, b=1000s/mm2, averages=2, scan time=6.5 min). A high-resolution T1-weighted structural dataset was collected (3D MP-RAGE, TR=1160 ms, TE=4.44 ms, FOV=230x230x170 mm^3, matrix=256x256x96, partitions=192, thickness=0.9 mm, scan time=5 min). DTI data was analyzed using TBSS from the FSL software package to localize differences in mean diffusivity (MD), factional anisotropy (FA), axial diffusivity ($\lambda_{||}$) and radial diffusivity ($\lambda_{\perp}$) between groups. VBM was performed in SPM using the VBM8 toolbox, using the default settings.

RESULTS: The DTI study revealed that MD is significantly increased (p-value < 0.03) for both Group A and Group B compared to controls. The tracts most affected were the callosal areas, the corona radiata, the right corticospinal tract, the longitudinal fasciculus, the forceps minor and the fronto-occipital fasciculus (Fig 1a). These changes are accompanied by an increase in $\lambda_{\perp}$ for both Group A and Group B vs controls (Fig 1b), while $\lambda_{||}$ does not show any significant changes. The VBM analysis showed loss of white matter in the corpus callosum for Group B compared to Group C (Fig 1c), while white matter loss is more diffuse (but still present) in Group A.

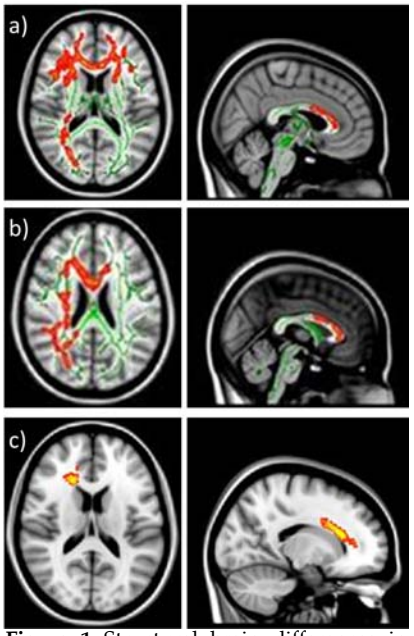

Figure 1 Structural brain differences in axial and sagittal plane. (a) MD differences between group B and C using TBSS (p<0.03). (b) $\lambda_{\perp}$ differences between group B and C using TBSS (p<0.03). (c) VBM volume loss in Group B vs Group C.

DISCUSSION/CONCLUSION: This study reveals that DTI and VBM can identify subtle early changes to the brains of HIV patients who do not yet exhibit cognitive impairment. MD and $\lambda_{\perp}$ were the most sensitive to neuropathological changes and occurs in areas of the brain that have been previously implicated in the literature [2-4]. The volume loss found in this study is localized to a small region, but this is unsurprising since atrophy has only previously been found in cognitively-impaired patients [6], while asymptomatic patients only report diffuse atrophy [7]. Although DTI differences are detected between both patient groups compared to controls, no significant differences are detected between the patient groups (A vs B). This suggests that either neurodegeneration occurs very early, before diagnosis and treatment has begun, or that treatment does little to prevent this process.

REFERENCES: [1] Ances BM, Curr Neurosci Rep. 2008;8:455. [2] Gongvatana A et al. J Neurovirol. 2009;15: 187-195. [3] Zhu T et al. J Neurovirol. 2012;19: 10. [4] Wu Y et al. AJNR. 2006;27: 656. [5] Dowell NG et al, NMR Biomed 2013;26:674. [6] Ge Y et al. AJNR Am J Neuroradiol. 2003;24:82. [7] Kuper M et al. J Neurol. 2011;258:1066.