Voxel-Based Morphometric Analysis of Brain Volumetry and Diffusivity in Hepatitis C

M. K. Sarma[1], R. Nagarajan[1], C. H. Hinkin[2], S. A. Castellon[2], J. P. Smith[3], H. Khanlou[4], L. Bhatti[4], J. Truong[5], E. Singer[6], J. Jang[7], M. Kim[7], G. Waterman[7], R. K. Gupta[8], and M. A. Thomas[1]

[1]Radiological Sciences, UCLA, Los Angeles, CA, United States, [2]Psychiatry and Biobehavioral Sciences, UCLA School of Medicine and VA Greater Los Angeles Healthcare System, Los Angeles, CA, United States, [3]VA Greater Los Angeles Healthcare System, Los Angeles, CA, United States, [4]AIDS Healthcare Foundation, Los Angeles, CA, United States, [5]Kaiser Permanente, Lancaster, CA, United States, [6]Neurology, UCLA School of Medicine, Los Angeles, CA, United States, [7]VA West Los Angeles Healthcare System, Los Angeles, CA, United States, [8]Radiological Sciences, SGPGIMS, Lucknow, UP, India

Introduction: Hepatitis C virus (HCV) infection is a rapidly increasing global health problem. Recent reports of cerebral dysfunction in chronic HCV infection have led to the suggestion that HCV may infect the central nervous system (CNS) (1). In this study we investigated the two diffusion parameters derived from diffusion tensor imaging (DTI), namely mean diffusivity (MD) and fractional anisotropy (FA), to look for the brain water changes using Voxel based morphometry (VBM), a method that allows comparisons at the group level. MD measures the rotationally invariant magnitude of water diffusion FA provides an index of directional selectivity of water diffusion (2). VBM has proved to be a powerful method in detecting regional differences in cerebral structure in various disorders. It provide the opportunity for an unbiased general search of abnormalities in the whole brain volume (3) and allow the detection of highly localized differences across the entire brain. The major goal of the study is to examine significant changes observed in MD, FA, gray matter (GM) and white matter (WM) in HCV infected patients across different regions of the brain.

Materials and Methods: We assessed nine patients with hepatitis C (mean age 56 years, range 51 to 65). They were compared to six healthy adult controls. 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) = 87 ms; average = 1] in the axial plane, with a 130 × 130 matrix size, 256 × 256 mm^2 field of view (FOV), 2.0 mm slice thickness, 72 slices. For each slice, diffusion gradients were applied along 64 independent orientations with b =1000 sec/mm^2 after the acquisition of b = 0 sec/mm^2 (b0) images. We also collected high-resolution T1-weighted images using a magnetization prepared rapid acquisition gradient echo (MPRAGE) pulse sequence (TR = 2200 msec; TE = 2.18 msec; inversion time = 900 msec; FA = 9°; matrix size = 256 x 256; FOV = 240 mm x 240 mm; slice thickness = 1 mm; number of slices = 176) for evaluation of structural brain abnormalities.

We used SPM5 to preprocess and analyse our data (4-6). Image preprocessing was carried out according to the optimized protocol described by Good et al. (7). For GM/WM analysis, the MPRAGE data sets were first normalized to the standard Montreal Neurological Institute (MNI) space template. The procedure then entailed a segmentation of the normalized images into GM, WM and CSF. The resulting GM/WM images were then smoothed with a Gaussian kernel of 10 mm fullwidth at half-maximum (FWHM). The MD and FA maps were calculated using the DTI Studio and normalized to the MNI template. For this procedure, T2-weighted images (b0 images) of each subject were normalized to the MNI template, using a priori-defined distributions of tissue types, and the resulting normalization parameters were applied to the corresponding MD and FA maps. The normalized MD and FA maps were smoothed using a Gaussian filter FWHM of 10 mm. Voxel-by-voxel analysis of covariance was used to compare volumetry and diffusivity measurements between patients and controls with age and sex as a covariate.

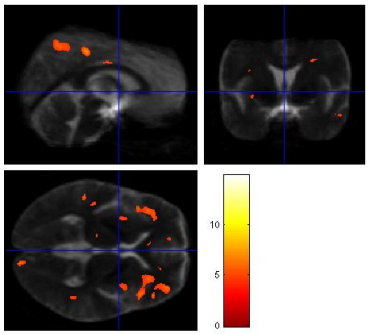

Figure 1: SPM analysis of MD value increase in patients compared to controls

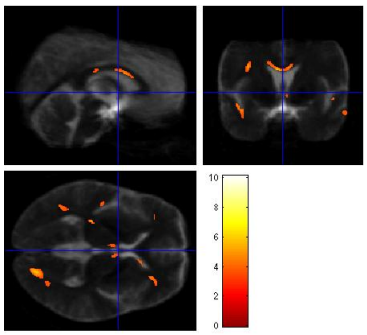

Figure 2: SPM analysis of FA value decrease in patients compared to controls

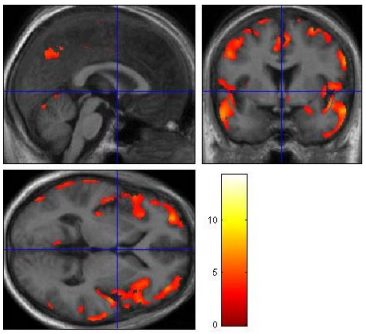

Figure 3: SPM analysis of gray matter volume decrease in patients compared to controls

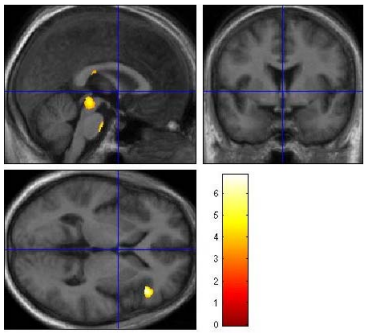

Figure 4: SPM analysis of white matter volume decrease in patients compared to controls

Results and Discussion: Statistical parametric MD and GM maps were thresholded with a false discovery rate (FDR) of $p<0.05$ and with minimum cluster size of 10 voxels (corrected for multiple comparisons). Statistical parametric FA and WM maps were thresholded with $p<0.005$ uncorrected for multiple comparisons and an extent threshold of 100 voxels.

Figure 1 shows regions with significantly increased MD values in patients compared with control subjects. Extensive changes were observed in bilateral frontal gray matter and frontal white matter, bilateral external capsule, temporal white matter, right occipital grey matter. Figure 2 shows regions of decreased FA values in patients compared to controls. The areas that showed reduced FA values are corpus callosum, right frontal white matter, occipital white matter. No regions showed higher MD and lower FA values in control subjects compared to patients.

Figure 3 and 4 shows regions of decreased gray and white matter volume in patients relative to control subjects. Widespread gray matter volume reduction was seen in the frontal, parietal and temporal regions. White matter volume decreases in the right frontal. corpus callosum and mid brain.

Conclusion: Our results showed widespread brain regions with increased MD values, indicating enhanced water content and decreased FA in Hepatitis C patients. We also observed decreased gray and white matter volume.

Acknowledgement: This research was supported by National Institute of Mental Health (NIMH) grants MH083553.

References:

1. Forton, D. M., J. M. Allsop, J. Main, G. R., et al. 2001; Lancet 358:38-39. 2. Beaulieu C. NMR Biomed 2002; 15: 435–455. 3. Ashburner J, Friston KJ. Neuroimage 2000; 11: 805–821 4. Ashburner J, Friston K. Neuroimage 1997; 6:209–17. 5. Friston KJ, Holmes A, Poline JB, et al. Hum Brain Mapp 1995; 2:189–210. 6. Wright IC, McGuire PK, Poline JB, et al. Neuroimage 1995; 2:244–52. 7. Good CD, Johnsrude IS, Ashburner J, et al. Neuroimage. 2001; 14:21–36.