Sustained Virologic Response Following Anti-HCV Pharmacotherapy is Associated with Improved Neurostructural Integrity: A DTI Study

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Introduction: Hepatitis C virus (HCV) is one of the most common chronic viral infections worldwide and is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma [1]. Neurological dysfunction has been observed in patients with HCV and growing body of evidence is showing that HCV may adversely affect cognition through direct central nervous system involvement [2]. The standard method for HCV treatment is a combination of pegylated interferon (IFN) alfa and ribavirin [3, 4], which can lead to a sustained viral suppression, notwithstanding adverse side effects. In this study we examined the two diffusion parameters derived from diffusion tensor imaging (DTI), namely mean diffusivity (MD) and fractional anisotropy (FA), across a group of HCV patients before and after IFN therapy using an automated atlas based analysis for regional parcellation that uses Large Deformation Diffeomorphic Metric Mapping (LDDMM) for non-linear registration. The use of LDDMM minimizes intra and inter-rater variability and improved the accuracy of the analysis. The primary aim of the current study was to compare FA and MD changes in different brain regions of HCV patients before and after IFN therapy.

Materials and Methods: Twelve HCV patients (age=55.8±5.2 years) treated with pegylated interferon with ribavirin for 36-60 weeks were examined before and after anti-HCV therapy. Out of the 12 patients, 3 were non-responder to IFN therapy and 2 were missing data regarding virologic response. We have used the remaining 7 patients for our diffusivity analysis. 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.

FA and MD were calculated using DtiStudio [5]. Before the normalization procedure, the skull was stripped using the b0 images and a skull-strip tool in RoiEditor software [6] using a modified version of the active contour method described by Chan and Vese [7]. A representation of the subsequent normalization process, performed using DiffeoMap [8]. 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) [9] was employed. The atlas-based analysis was performed using a WM parcellation map (WMPM) [10]. 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. Statistical analyses were done by paired t-test and significance was determined with a p value of 0.05.

Regions	Before IFN		After IFN		p- value
	Mean	SD	Mean	SD	
Putamen left	0.258	0.009	0.272	0.012	0.024
Putamen right	0.280	0.012	0.301	0.015	0.011
Amugdala right	0.231	0.010	0.261	0.027	0.037
Uncinate fasciculus right	0.332	0.014	0.350	0.020	0.008
Fusiform gyrus left	0.272	0.019	0.288	0.022	0.035
Superior parietal lobule left	0.369	0.014	0.357	0.010	0.003
Superior frontal gyrus left	0.344	0.012	0.333	0.014	0.047
Postcentral gyrus left	0.351	0.015	0.340	0.012	0.013
Posterior limb of internal capsule left	0.538	0.021	0.525	0.018	0.020
Precentral gyrus right	0.358	0.015	0.346	0.010	0.022
Middle fronto-orbital gyrus right	0.295	0.024	0.278	0.015	0.007
Inferior cerebellar peduncle right	0.400	0.034	0.379	0.032	0.042
Cingulum right	0.392	0.022	0.361	0.031	0.033
Postcentral gyrus right	0.346	0.017	0.336	0.017	0.038

Table 1: Regions with significant ($p<0.05$) FA changes in HCV patients before IFN compared to after IFN.

Results and Discussion: Table 1 shows the results of FA changes. We found statistically significant increases in FA in bilateral putamen, right amygdala, uncinate fasciculus, and left fusiform gyrus in patients after IFN compared to before IFN. We also identified a decrease in the FA in bilateral postcentral gyrus, the following regions on the right: inferior cerebellar peduncle, cingulum, precentral gyrus, middle fronto-orbital gyrus, and the following left sided regions left: superior parietal lobule, superior frontal gyrus, posterior limb of internal capsule.

Changes in MD are shown in Table 2. Significant decreases in MD were observed in bilateral globus pallidus, right fornix/stria terminalis, putamen, thalamus, cerebral peduncle, and left caudate nucleus. Significant increase in MD values was also found in two regions: right precentral gyrus and pre-cuneus.

Conclusion: This study demonstrated brain diffusivity differences before and after anti-HCV therapy with primarily decreased MD and increased/decreased FA values in multiple brain regions following anti-HCV therapy. Our results suggest that HCV eradication has a beneficial effect on cerebral integrity, and is an important factor when contemplating anti-viral therapy in HCV. Further studies are required to validate the current findings and determine the extent to which cerebral improvements correlate with clinical markers of brain function, such as neuropsychological testing. Further, DTI may prove to be a sensitive tool for examining HCV-associated neurological dysfunction and also monitoring changes in brain function following anti-HCV therapy.

Regions	Before IFN ($x10^{-3}$ mm^2/s)		after IFN ($x10^{-3}$ mm^2/s)		p- value
	Mean	SD	Mean	SD	
Fornix/Stria terminalis right	0.973	0.043	0.723	0.040	0.021
Putamen right	0.671	0.035	0.607	0.038	0.034
Thalamus right	0.826	0.017	0.775	0.045	0.013
Globus Pallidus right	0.650	0.065	0.514	0.058	0.009
Globus Pallidus left	0.673	0.036	0.539	0.044	0.031
Cerebral peduncle right	0.781	0.096	0.613	0.138	0.007
Caudate Nucleus left	0.847	0.036	0.777	0.092	0.001
Precentral gyrus right	0.696	0.015	0.708	0.018	0.016
Pre-cuneus right	0.689	0.024	0.708	0.034	0.017

Table 2: Summary of significant ($p<0.05$) MD values changes in patients before, and after IFN therapy derived from different regions of the brain.

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