A Magnetic Resonance Imaging Study of Cortical Thickness and Volumetric Changes in Hepatitis C: Before and After Interferon Therapy

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Introduction: Hepatitis C virus (HCV) is one of the most common chronic viral infections worldwide and is a major cause of cirrhosis and hepatocellular carcinoma [1]. Neurological dysfunction has been observed in patients with HCV and is presumed to result from infected monocytes and macrophages that cross the blood brain barrier. The standard method for HCV treatment is a combination of pegylated interferon (IFN) alfa and ribavirin [2, 3], which can lead to a sustained viral suppression, notwithstanding adverse side effects. In this study we examined the cortical thickness and volume across a group of HCV patients before and after IFN therapy employing an automated method for regional parcellation that uses curvature landmarks and gray matter (GM)/WM surface boundary information. A cortical surface-based analysis of the whole cortical mantle obtained from volumetric magnetic resonance imaging (MRI) data was done. The major goal of the study is to compare cortical thickness (CT) and volumetric changes in the cortex of HCV patients before, and after IFN therapy.

Materials and Methods: Seven patients with histologically-defined chronic hepatitis C were recruited from a viral hepatitis clinic (mean age 58.5 years, range 51 to 65) were recruited for this study. All subjects gave informed consent according to an institutionally approved research protocol. All patients were initially treated with interferon alfa and ribavirin for 48 weeks. A Siemens 3T Trio-Tim MRI scanner (Siemens Medical Solution, Erlangen, Germany) was used and a 3D structural MRI was acquired on each subject using a T1-weighted a magnetization prepared rapid acquisition gradient echo (MPRAGE) 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.

Cortical reconstruction and volumetric segmentation was performed with FreeSurfer software [4,5]. Briefly, processing consisted of motion correction and averaging of multiple volumetric T1 weighted images, removal of non-brain tissue [6], automated Talairach transformation, automatic segmentation of the subcortical white matter and deep gray matter structures [7], tessellation of the gray/white matter boundary, inflation of the folded surface tessellation, automatic correction of topological defects and the extraction of cortical surfaces. Estimates of cortical thickness were made by measuring the shortest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface and averaging between these two values. Subsequent to cortical reconstruction, the cortex is subdivided into 34 units based on gyral and sulcal structures [8]. These parcellations were subsequently used to assign a label to the underlying subcortical WM. Furthermore, Freesurfer produces a table of statistical measures such as the intracranial volume.

Results and Discussion: We conducted MANCOVA analyses on the 34 parcellations in each hemisphere with age, and cerebral volume (volumes of the cerebral cortex on the left and right hemisphere) as covariate to compare CT and cortical volume (CV) before and after IFN. We corrected all group comparisons for multiple comparisons using a Bonferroni correction. Table 1 shows the results of CT changes. We found statistically significant increases in CT in bilateral occipital in patients after IFN compared to before IFN. We also identified an increase in the CT within additional areas, although these did not reach significance after correcting for the number of tests.

Changes in CV are shown in Table 2. Significant increase in CV were observed in both hemisphere at the caudal middle frontal, rostral middle frontal, and superior temporal in patients after IFN compared to before IFN. CV also increases in left precentral, left lateral orbitofrontal, and right middle temporal. The areas that showed significant reduced CV in patients after IFN compared to before IFN were left medial orbitofrontal, right fusiform and bilateral occipital.

Regions	Before IFN (mm^3)	After IFN (mm^3)	F	p
Left				
Caudal middle frontal	6124±1374.1	6366.5±1395.4	19.5	**<0.001**
Isthmus cingulate	2835.7±552.8	2899.7±571.0	12.0	0.001
Postcentral	10035.4±1745.9	10339.2±1757.1	14.9	0.001
Precentral	12754.1±2164.6	12916.2±1893.9	19.9	**<0.001**
Precuneus	9676.7±1096.9	9698.2±1042.5	8.6	0.004
Rostral middle frontal	12899.4±1773.6	12942.2±1558.4	24.5	**<0.001**
Superior temporal	10831±1141.0	10875.2±981.1	29.5	**<0.001**
Insula	6570.4±829.5	6611.7±636.0	3.9	0.044
Lateral occipital	12306.1±2832.1	12196±2754.6	31.6	**<0.001**
Medial orbitofrontal	5106.6±1080.5	5025.2±843.1	26.0	**<0.001**
Fusiform	10232.3±1653.9	10067.3±1773.8	6.7	0.009
Right				
Caudal anterior cingulate	1879±441.8	1925.13±440.6	6.6	0.01
Caudal middle frontal	5818.1±919.0	5846±967.7	37.0	**<0.001**
Lateral orbitofrontal	6514.3±762.6	6675.4±806.4	32.4	**<0.001**
Middle temporal	11642.1±1538.6	12057.3±1649.6	22.9	**<0.001**
Precuneus	9810.3±1292.1	9909.7±1226.8	9.4	0.003
Rostral middlefrontal	14064±2647.3	14395.8±2242.7	20.2	**<0.001**
Superior frontal	19695.4±2350.7	19906.4±2295.3	7.7	0.006
Superior temporal	10326.7±1290.4	10349.6±1248.2	26.3	**<0.001**
Fusiform	9260.3±1871.6	9125.6±1958.6	15.0	**<0.001**
Lateral occipital	11759.9±2223.9	11626.4±2255.7	82.5	**<0.001**

Table1 2: Regional cortical volumetric changes in patients before IFN compared to after IFN. Cortical regions significant at Bonferroni's corrected threshold of p <0.0016 are highlighted in bold.

Regions	Before IFN (mm)	After IFN (mm)	F	p
Left hemisphere				
Caudal anterior cingulate	2.50±0.35	2.53±0.30	4.2	0.036
Entorhinal	3.26±0.27	3.29±0.32	5.8	0.014
Lateral occipital	2.23±0.12	2.24±0.11	21.1	**<0.001**
Rostral anterior cingulate	2.64±0.22	2.67±0.24	3.9	0.044
Right hemisphere				
Isthmus cingulate	2.44±0.22	2.45±0.27	7.3	0.007
Lateral occipital	2.21±0.10	2.22±0.12	22.5	**<0.001**
Rostral anterior cingulate	2. 60±0.16	2.64±0.21	7.3	0.007
Transverse temporal	2.30±0.14	2.35±0.11	4.1	0.038

Table1 1: Regional CT changes in patients before IFN compared to after IFN. Cortical regions significant at Bonferroni's corrected threshold of p <0.0016 are highlighted in bold.

Conclusion: This study demonstrated cortical thickness and volumetric differences between patients before and after interferon therapy. We found a significant increase in cortical thickness in the lateral occipital region in both hemisphere. We also observed widespread changes in cortical volume. Further studies are required to validate and elaborate these findings. Nevertheless, this study suggests utility of morphometric study in investigating cortical thickness and volume in HCV patients to evaluate the effect of interferon therapy.

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