HIV/HCV co-infection and HCV mono-infection are associated with subcortical and cortical atrophy

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Introduction: Co-infection with the Human Immunodeficiency Virus (HIV) and Hepatitis C virus (HCV) is a significant problem with almost 30% of HIV infected individuals also HCV co-infected [1]. Both viruses have similar routes of transmission and are capable of crossing the blood-brain barrier [2] resulting in neuropathological changes and brain inflammation. Cognitive impairment was previously thought to result from cirrhosis-associated hepatic encephalopathy. Recent evidence, however, suggests that approximately one-third of people with chronic HCV experience cognitive impairment [3] even in the absence of cirrhosis and that its occurrence is unrelated to other indices of liver function. While the use of neuroimaging techniques such as Magnetic Resonance Spectroscopy have helped to identify metabolite abnormalities in regions such as the basal ganglia, little is known about how the co-infection affects other brain regions, including which cortical regions are differentially affected. The current study sought to investigate cortical thickness and subcortical structure volume across a group of HCV/HIV co-infected, HCV mono-infected and healthy adults employing an automated method for regional parcellation that uses curvature landmarks and gray matter (GM)/white matter (WM) surface boundary information. We conducted a cortical surface-based analysis of the whole cortical mantle obtained from volumetric magnetic resonance imaging (MRI) data. The main objective of the study is to compare measures of cortical thickness and subcortical structure volume between HCV mono-infected, HIV/HCV co-infected, and healthy controls.

Materials and Methods: We assessed 16 HCV mono-infected (age 56.7y ± 4.9) and 11 HCV/HIV co-infected patients (age 51y ± 9.4). They were compared to 15 uninfected controls (age 50.5y ± 10.6). 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 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.

We used FreeSurfer Image Analysis Suite [4, 5] for cortical reconstruction and volumetric segmentation. 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, statistical thickness difference maps were constructed using a t statistic. We used a General Linear Model (GLM) in which the main effects of group (thickness differences between HCV mono-, HCV/HIV co-infected and control adults) are shown.

Results and Discussion: The GLM analyses of cortical thickness (CT) in both hemisphere were conducted by paired-wise comparison of HIV/HCV co-infected and HCV mono-infected group to healthy control by using the multiple comparisons Monte Carlo simulation to make inferences at a p value of 0.001. We used a contrast [1 -1 0 0 0 0] to regress out age and gender factors. Significant regions in this study included clusters at each location which were uncorrected for FDR with a surface area of more than 25 mm^2 are reported. We found numerous regions in which HIV/HCV co-infected and HCV mono-infected patients had thinner cortices compared to controls ($p < 0.01$ uncorrected) (Figure 1). Statistically significant cortical thinning was observed in the HIV/HCV co-infected group in lateral occipital gyrus of both hemisphere, postcentral gyrus of the left hemisphere and superior temporal gyrus of the right hemisphere ($k > 50$ mm2, $p < 0.001$, uncorrected). When HCV mono-infected group was compared to control subjects, we observed significant decrease of cortical thickness in lateral orbitofrontal, caudal mid-frontal and superior frontal in the left hemisphere and rostral mid-frontal in the right hemisphere.

We conducted MANCOVA analyses on the subcortical parcellations in each hemisphere with age and total intracranial volume (TIV) as covariates to compare subcortical GM volume (GMV) of HCV mono- and HIV/HCV co-infected patients with healthy adults. We corrected all group comparisons for multiple comparisons using a Bonferroni correction. Table 1 shows the results of subcortical GM volume changes. Significant decrease in volume were observed in bilateral left caudate, 4th ventricle, right caudate, right hippocampus, posterior corpus callosum (CC), and anterior CC in HIV/HCV co-infected patients compared to healthy adults. When HCV mono-infected patients were compared to healthy adults, we found decreases in subcortical GMV in bilateral putamen, left choroid plexus, right hippocampus, posterior CC, and anterior CC. We also observed left and right cerebral GMV decrease in HCV mono-infected patients, though this was not statistically significant.

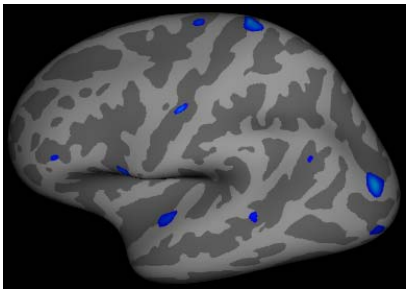

Figure 1: An inflated surface representation of cortical P value representing thickness (light and dark blue are areas of reduced thickness in HCV/HIV co-infected patients compared to healthy adults).

Regions	Controls		HCV/HIV co-Infected		HCV mono-infected	
	Mean	SD	Mean	SD	Mean	SD
Left-Caudate	0.0024	0.0002	0.0023	0.0002	0.0022	0.0003
Left-Putamen	0.0037	0.0003	0.0037	0.0003	0.0034	0.0003
4th-Ventricle	0.0012	0.0003	0.0010	0.0002	0.0012	0.0004
Left-choroid-plexus	0.0012	0.0002	0.0012	0.0002	0.0010	0.0002
Right-Caudate	0.0026	0.0002	0.0024	0.0002	0.0024	0.0004
Right-Putamen	0.0038	0.0005	0.0037	0.0003	0.0033	0.0004
Right-Hippocampus	0.0030	0.0003	0.0027	0.0002	0.0027	0.0003
CC_Posterior	0.0007	0.0001	0.0006	0.0001	0.0006	0.0002
CC_Anterior	0.0006	0.0001	0.0006	0.0001	0.0005	0.0001
Left cerebral GMV	0.1538	0.0095	0.1516	0.0087	0.1478	0.0075
Right cerebral GMV	0.1544	0.0110	0.1514	0.0097	0.1474	0.0086

Table1 1: Subcortical regions significant at Bonferroni's corrected threshold of $p < 0.0016$. Data are reported as mean normalized volumes (mm^3).

Conclusion: Our results showed widespread brain regions with cortical thinning in HCV/HIV co-infected and HCV mono-infected adults relative to healthy controls, which is consistent with studies that have demonstrated neurobehavioral impairments associated with both HIV and Hepatitis C. We also observed subcortical gray matter volume changes between healthy control and HCV/HIV co-infected, HCV mono-infected adults, suggesting that subcortical structures may be highly sensitive to the neuropathological changes associated with HCV.

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