2D MRS COMBINED WITH PROFIT ALGORITHM IS SENSITIVE TO HCV ASSOCIATED CEREBROMETABOLIC ABNORMALITIES

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Introduction The central nervous system (CNS) serves as a reservoir for the Hepatitis C virus (HCV) once it crosses through the blood-brain barrier**.** Neurocognitive deficits in attention, processing speed, and memory are commonly observed among infected patients (1). While magnetic resonance spectroscopy (MRS) studies of HCV have identified N-acetylaspartate (NAA), Myo-Inositol (mI), and Choline (Cho) as important cerebral markers of inflammation and cell function (2,3), the role of neurotransmitters such Gama amino butyric acid (GABA) and Glutathione (GSH) have received less attention in the literature. GABA is an inhibitory neurotransmitter that, among other roles, is essential for mental concentration and focus, whereas GSH is an antioxidant that protects the brain against oxidative stress. While Proton ((^{1}H) MRS has been used to assess the metabolic changes in the brain in patients with HCV, the goal of the present study was to employ an emerging MRS approach - two-dimensional (2D) localized correlated spectroscopy (L-COSY) – and combine that with a prior knowledge fitting (ProFit) algorithm to better characterize and quantify cerebral metabolite abnormalities present in HCV+ patients versus healthy controls.

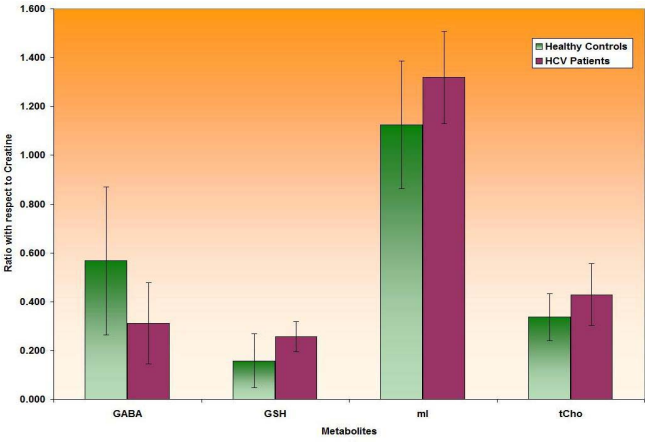
Methods: Fourteen patients with advanced HCV disease (mean age of 56.2 years) and ten healthy controls (mean age of 46.6 years) were recruited for this MRI/MRS study. The entire protocol was approved by the institutional review board (IRB), and informed consent was obtained from each human subject. A 2D L-COSY sequence containing three slice-selective radiofrequency (rf) pulses (90^0, 180^0, 90^0) was implemented on a Siemens 3T Trio-Tim scanner (Siemens Medical Systems, Germany). The following parameters were used: TR/TE=2s/30ms, 3x3x3cm^3 voxel, 8 averages per Δt_1 and 100 Δt_1 increments. The voxel was placed in the left frontal lobe. The 12 channel coil was used for the hepatitis MR study. The Prior Knowledge Fitting (ProFit) algorithm has been developed for the quantitation of 2D L-COSY (4). The ProFit algorithm uses MATLAB (Mathworks, Natick, MA, USA, ver. 7.3) and was executed on an Intel 2.8GHz with Windows XP. ProFit algorithm uses prior knowledge constraints and a combined linear and non-linear optimization for fitting concentrations. The algorithm uses a prior knowledge basis set generated using the GAMMA library (5) in combination with the chemical shift and J-coupling values reported the literature (6). Based on prior research that has implicated frontal white matter as a brain region as particularly sensitive to the adverse effects of HCV, we confined our analyses to this region.

Results and Discussion: Table 1 shows metabolites ratios with respect to creatine recorded using 2D L-COSY in the left frontal white/gray matter region. Figure 1 shows significant metabolites changes between healthy controls and HCV patients. 2D L-COSY combined with ProFit algorithm quantified the following metabolites: (N-acetylaspartate (NAA), creatine (Cr), glycerylphosphocholine (GPC), phosphorylcholine (PCh), alanine (Ala), aspartate (Asp), gamma-aminobutyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glutathione (GSH), myo-inositol (mI), N-acetylaspartylglutamate (NAAG), phosphoethanolamine (PE), taurine (Tau) and scyllo-inositol (Scy). HCV+ participants demonstrated significant elevations of GSH, mI, total choline (GPC+PCh+Cho) and decreased GABA compared to healthy controls ($p < 0.05$). Choline peaks likely represent various cell membrane precursor and breakdown products, including PCh, and GPC. Though there was a trend towards lower levels of NAA in the HCV+ group, this was not statistically significant. The elevation of mI is hypothesized to reflect HCV associated glial activation. Altered GABA levels may also exert an adverse impact on neurological function.

Table 1. 2D L-COSY frontal white metabolites ratios with respect to creatine

Metabolites	Controls (n=10) Mean ± SD	Patients (n=14) Mean ± SD
NAA	1.218±0.288	1.181±0.193
GPC	0.150±0.081	0.156±0.035
PCh	0.194±0.066	0.169±0.032
Ala	0.325±0.343	0.183±0.116
Asp	0.421±0.175	0.442±0.082
GABA††	**0.568±0.303**	**0.311±0.166**
Glc	0.299±0.237	0.349±0.187
Gln	0.217±0.239	0.296±0.143
Glu	1.621±0.303	1.636±0.211
GSH††	**0.158±0.111**	**0.257±0.061**
mI††	**1.124±0.262**	**1.318±0.189**
PE	0.524±0.385	0.391±0.076
Tau	0.258±0.193	0.269±0.096
Scy	0.077±0.041	0.089±0.037
NAA+NAAG	1.471±0.321	1.300±0.188
GPC+PCH+Cho††	**0.337±0.095**	**0.429±0.127**
Gln+Glu	1.877±0.234	1.869±0.191

Figure 1. Significant metabolites changes between healthy controls and HCV patients



†† **p value < 0.05**

Conclusion: Elevations in GSH may represent oxidative stress in the brain, whereas decreases in GABA suggest a dysregulation in inhibitory processes required for efficient cognitive functioning. Furthermore, 2D L-COSY using ProFit algorithm may better detect GSH and GABA compared to 1-D MRS algorithm.

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References:

1. Forton DM, Allsop JM, Cox IJ et al. AIDS. 2005 Oct;19 Suppl 3:S53-63.
2. Mader I, Rauer S, Gall P, et al. Eur J Radiol 2008;67:250-7.
3. Forton DM, Allsop JM, Main J, et al. Lancet 2001; 358:38-39.
4. Frias-Martinez, E Rajakumar N, Liu X , et al. ISMRM 2008; Pp 691.
5. Smith SA, Levante TO, Meier, BH, et al. J. Magn. Reson. 1994; 106: 75-105.
6. Govindaraju V, Young K and Maudsley AA. NMR Biomed 2000; 13: 129-53.