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# Improvements in brain and behavior following eradication of hepatitis C

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**Abstract** Despite recent advances in treatment, hepatitis C remains a significant public health problem. The hepatitis C virus (HCV) is known to infiltrate the brain, yet findings from studies on associated neurocognitive and neuropathological changes are mixed. Furthermore, it remains unclear if HCV eradication improves HCV-associated neurological compromise. This study examined the longitudinal relationship between neurocognitive and neurophysiologic markers among healthy HCV− controls and HCV+ adults following successful HCV eradication. We hypothesized that neurocognitive outcomes following treatment would be related to both improved cognition and white matter integrity. Participants included 57 HCV+ participants who successfully cleared the virus at the end of treatment (sustained virologic responders [SVRs]) and 22 HCV− controls. Participants underwent neuropsychological testing and, for a nested subset of participants, neuroimaging (diffusion tensor imaging) at baseline and 12 weeks following completion of HCV therapy. Contrary to expectation, group-level longitudinal analyses did not reveal significant improvement in neurocognitive performance in the SVRs compared to the control group. However, a subgroup of SVRs demonstrated a significant improvement in cognition relative to controls, which was related to improved white matter integrity. Indeed, neuroimaging data revealed beneficial effects associated with clearing the virus, particularly in the posterior corona radiata and the superior longitudinal fasciculus. Findings suggest that a subgroup of HCV+ patients experienced improvements in cognitive functioning following eradication of HCV, which appears related to positive changes in white matter integrity. Future research should examine whether any additional improvements in neurocognition and white matter integrity among SVRs occur with longer follow-up periods.

**Keywords** Hepatitis C virus · Neurocognition · Neuropathology · Diffusion tensor imaging · White matter integrity · Sustained virologic response

Hepatitis C virus (HCV) is a neurotropic virus that is associated with neuropsychiatric disorders. However, it is unclear if HCV eradication improves HCV-associated neurological compromise.

HCV is known to have direct effects on the central nervous system (CNS), as studies have detected HCV in brain tissue (Forton et al. 2004) and in cerebrospinal fluid (e.g., Laskus et al. 2002; Tully et al. 2016). Accordingly, investigators have shown evidence of neurocognitive dysfunction associated with HCV (e.g., Forton et al. 2006). Cognitive impairments were previously thought to be associated with the development of hepatic encephalopathy (e.g., Gaeta et al. 2013; Shawcross and Jalan 2005). However, neurocognitive deficits have been demonstrated in the absence of advanced liver disease or hyperammonemia (Forton et al. 2006; Hilsabeck et al.

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2003; Hinkin et al. 2008; Posada et al. 2009), as well as the absence of HIV co-infection, depression, or substance abuse (Cherner et al. 2005).

HCV within the CNS appears to be compartmentalized in the frontal cortex, basal ganglia, and centrum semiovale (Córdoba et al. 2003). Accordingly, deficits in attention, concentration, psychomotor speed, and verbal fluency among HCV+ individuals have been most frequently reported (Hilsabeck et al. 2003; Hinkin et al. 2008; Letendre et al. 2007; Clifford et al. 2009; Soogoor et al. 2006; Thein et al. 2007). However, other studies (e.g., Lowry et al. 2016; McAndrews et al. 2005) have failed to detect neurocognitive deficits associated with HCV infection (e.g., Lowry et al. 2016). These studies have generally paid close attention to potentially confounding causes of impairment, such as injection drug use (Zeuzem 2008), history of head trauma (Kraus et al. 2013), and HCV RNA levels (e.g., Forton et al. 2002; Kraus et al. 2013; Lowry et al. 2016). As a result, there is not a clear consensus regarding the impact of HCV-associated neurocognitive and neurobehavioral effects. However, several studies have shown that the neuropsychological manifestations of HCV are subtle (e.g., performance < 1.5 SD below the normative standard across the majority of cognitive tests included) after accounting for such potentially confounding factors (e.g., Grover et al. 2012; Weissenborn et al. 2004).

While largely supplanted by newer drug regimens, pegylated alfa interferon and ribavirin (PEG-IFN/RBV), first used in the late 1980s, had proven to be an effective combination treatment for some individuals with HCV that resulted in HCV clearance or a sustained virologic response (SVR; Bladowska et al. 2013a). SVR has been shown by some studies (Bladowska et al. 2013b; Forton et al. 2002) though not all (e.g., Huckans et al. 2015; Lowry et al. 2016; McAndrews et al. 2005) to result in improvement in neurocognitive performance. While the mechanism remains unclear, there is reason to believe that successful treatment of HCV could result in improved neurocognitive function, though it remains possible that some of the improvements may be attributable to the nature of open-label trials and/or practice effects associated with repeat testing, for example.

Less is known about the pre- versus post-treatment neuroanatomic and associated neurocognitive changes that may occur among SVR patients, though studies have reported improved metabolic function in the putamen and left occipital lobe (Juengling et al. 2000) as well as the basal ganglia (Byrnes et al. 2012). Byrnes et al. (2012) also reported improved verbal learning, memory, and visuospatial skills in the HCV-clearing group; however, they did not relate their neuroimaging findings to these cognitive changes. Clearly, further research is needed to help determine the extent to which HCV impacts neurocognitive performance and neuroanatomical changes over the course of treatment and after successful clearance of the virus.

This longitudinal study was designed to determine if successful eradication of HCV resulted in improvements in cognitive function and white matter integrity. We examined changes in neuropsychological test performance and DTI parameters in HCV+ individuals who successfully responded to treatment and achieved an SVR and HCV− controls. We hypothesized that neurocognitive outcomes following treatment would be related to improved cognition and improved white matter integrity and that those SVR participants who demonstrated the greatest degree of cognitive improvement would also demonstrate greater improvement in white matter integrity as indexed by DTI parameters.

## Methods

### Participants

All procedures were approved by the University of California, Los Angeles and VA Greater Los Angeles Healthcare System Institutional Review Boards. All HCV+ participants in this study met clinical criteria for undergoing HCV treatment (Hennes et al. 2008). None of the HCV+ participants had begun treatment at the onset of the study and all began treatment after the baseline evaluation. All participants provided written informed consent prior to entering the study. Inclusion criteria were: (a) 18 years of age or older, (b) proficient at reading and writing in English, and (c) reading proficiency at or above the 6th grade level. Exclusion criteria were: (a) cirrhosis/liver failure assessed via blood tests or liver biopsy with model for end-stage liver disease (MELD) score > 12; (b) current or past psychotic spectrum disorder; (c) current moderate or severe major depressive disorder; (d) history of learning disorder, neurologic disorder (e.g., seizure disorder, stroke), head injury with loss of consciousness equal to or greater than 30 min, or any neurologic disease; (e) concurrent hepatitis A or B infection; (f) diagnosis of HIV as assessed via seropositive HIV antibody testing; (g) recent illicit drug use as assessed via urine toxicology; and (h) contraindication for MRI. Treatment adherence to PEG-IFN/RBV was monitored using MEMS caps. Treatment adherence to interferon was monitored using weekly phone calls while the participant was self-administering the injections. Non-adherence as well as participant/physician-directed treatment discontinuation resulted in exclusion from analyses.

After exclusion criteria were applied at the beginning of the study and after accounting for attrition across the longitudinal portion of the study, our final sample included 57 HCV+ participants who successfully cleared the virus at the end of therapy and 22 controls. All healthy controls were local, community dwelling individuals. Within this sample, a nested sample of participants completed DTI at baseline and at follow-up (HCV+ $N = 12$, control $N = 10$). Participants underwent

neuropsychological testing and, for a nested subset of participants, neuroimaging, at baseline and 12 weeks after completion of HCV treatment (i.e., follow-up).

## Measures

### *Neurocognitive function*

Participants completed a comprehensive neuropsychological test battery, which we used to assess neurocognitive function both at the global and domain levels. We measured six cognitive domains: (1) *Attention*—Wechsler Adult Intelligence Scale—Third Edition (WAIS-III) Letter–Number Sequencing subtest (Wechsler 1997), Paced Auditory Serial Addition Test (only the first 50 trials; Gronwall 1977), and the MATRICS Continuous Performance Test (mean detectability; Nuechterlein et al. 2008); (2) *Processing speed*—WAIS-III Digit Symbol and Symbol Search subtests (Wechsler 1997), Trail Making Test—Part A (Reitan 1958), and Stroop Color Naming and Word Reading (Stroop 1935); (3) *Learning and memory*—Hopkins Verbal Learning Test—Revised (Shapiro et al. 1999) and Brief Visuospatial Memory Test—Revised (Benedict 1997); (4) *Language/verbal fluency*—Controlled Oral Word Association Test (FAS and Animals; Benton et al. 1994); (5) *Executive function*—Trail Making Test—Part B (Reitan 1958) and Stroop Color–Word Interference Test (Stroop 1935); and (6) *Motor speed*—Grooved Pegboard Test (dominant and non-dominant hands; Kløve 1963). We converted raw test scores into *demographically-adjusted T* scores and then averaged them to create neurocognitive domain *T* scores. We calculated the global neurocognition score by averaging the *T* scores from all of the neuropsychological test variables.

We chose a method for operationalizing "clinically significant" improvement that was determined in the initial grant application in order to limit subjectivity and based largely on AIDS Clinical Trial Group, Neurological AIDS Research Consortium (Price et al. 1999), and University of California, San Diego HNRC clinical trials (e.g., Carey et al. 2004). For our study, clinically significant improvement was defined a priori as a test–retest improvement in excess of the mean plus 0.5 SD, relative to the control group's change score.

### *Neuroimaging acquisition and processing*

High-resolution T1-weighted structural and diffusion-weighted MRI (i.e., DTI) were collected using a 3-T Trio MRI scanner (Siemens Medical System, Erlangen, Germany). T1-weighted images were acquired using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) sequence with the following parameters: repetition time (TR)/echo time (TE) = 2220/2.2 ms, inversion time = 900 ms, average = 1, matrix size = 256 × 256, field of view (FOV) = 240 × 240 $mm^2$, slice thickness = 1 mm, number of slices = 176. DTI was acquired via single-shot echo-planar dual spin echo sequence and ramp sampling (TR = 9600 ms, TE = 90 ms, flip angle = 90°, average = 1). Using an image matrix of 130 × 130, 71 axial sections were acquired with slice thickness = 2 mm with no interslice gap and an FOV of 256 × 256 $mm^2$. For each slice, diffusion gradients were applied along 64 independent directions with $b$ = 1000 s/$mm^2$ after the acquisition of $b$ = 0 s/$mm^2$ ($b0$) images.

DTIStudio, ROIEditor, and Diffeomap (available at www.MriStudio.org) were used for post-processing the DTI data. Fractional anisotropy (FA) and mean diffusivity (MD) maps were created using DTIStudio followed by skull stripping using the $b0$ images and a skull-strip tool available in RoiEditor software. Images were nonlinearly transformed to JHU-MNI-SS space using dual contrast large deformation diffeomorphic metric mapping. The brain was segmented into 130 white and gray matter regions using white matter parcellation maps with an FA threshold of ≥0.25.We focused our analyses on white matter regions including the external capsule, anterior corona radiata, superior corona radiata, posterior corona radiata, posterior thalamic radiation, anterior limb of the internal capsule, posterior limb of the internal capsule, superior longitudinal fasciculus, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, fornix and stria terminalis, as well as the genu, body, and splenium of the corpus callosum. At the current resolution, the fornix and stria terminalis could not be segmented and so were included as one continuous ROI. Left and right hemisphere FA and MD values for each ROI were averaged to create bilateral FA and MD variables for further investigation.

## Statistical analysis

Repeated Measures ANOVAs (RMANOVAs) were employed to evaluate whether the HCV+ participants who successfully cleared the virus at the end of therapy —termed Sustained Virologic Responders (SVRs)—and HCV− control groups demonstrated differential improvement in cognition over time with global and domain level mean *T* scores as the outcome variable of interest. We applied the same ANOVA-based statistical analysis paradigms to the neuroimaging data. RMANOVAs were run to determine whether the SVR group demonstrated improvements in white matter integrity (FA and MD in the above described regions) from baseline to study completion (12 weeks after completion of treatment) relative to controls. False Discover Rate (FDR) was used to correct for multiple comparisons. We then conducted correlation analyses to determine whether absolute change in domain level (e.g., attention, working memory) and global cognitive performance were associated with absolute change in white matter

integrity (FA and MD), separately, in the SVR and control group.

Finally, multivariate analyses of variance (MANOVA) were conducted to determine whether the SVRs who demonstrated a clinically significant degree of improved neurocognition displayed differential change in white matter integrity (absolute change in FA and MD) versus SVRs whose cognitive function did not improve. These analyses were confined to ROIs that were significant in previous analyses. Increases in FA and decreases in MD over time were interpreted as improvements.

## Results

### Sample characteristics

Table 1 provides descriptive statistics for key demographic variables.

For our entire sample at baseline, there were no significant differences across groups in terms of years of education or ethnicity. However, there were significantly more women in the control group ($\chi^2 = 4.74$, $p = 0.029$). There were no significant differences in age, gender, education, or race/ethnicity between the nested groups (HCV SVR and controls) that completed neuroimaging at baseline and follow-up (all $p$s > 0.05). There were also no significant differences (all $p$s > 0.10) between the two SVR groups (those with and without longitudinal change in cognition) in terms of age, gender, education, race/ethnicity, baseline neurocognitive performance, liver disease severity (MELD score), or current psychiatric functioning (depression, anxiety).

**Table 1** Descriptive statistics for demographic variables

| Variable | Controls ($n$ = 22) | | SVRs[b] ($n$ = 57) | |
|---|---|---|---|---|
| | *M* | *SD* | *M* | *SD* |
| Age (years at baseline) | 51.82 | 7.27 | 53.26 | 7.60 |
| Education (years) | 13.68 | 1.78 | 12.79 | 2.01 |
| 0.5 | | | | |
| | *n* | % | *n* | % |
| Female gender[a] | 9* | 40.9 | 10 | 17.5 |
| Ethnicity | | | | |
| Black/African American | 7 | 31.8 | 11 | 19.3 |
| Hispanic | 6 | 27.3 | 8 | 14.0 |
| Non-Hispanic White | 9 | 40.9 | 36 | 63.2 |
| Asian/Pacific Islander | 0 | 0.0 | 0 | 0.0 |
| American Indian/Alaskan Native | 0 | 0.0 | 1 | 1.8 |
| Other/multiethnic | 0 | 0.0 | 1 | 1.8 |
| MELD score | N/A | N/A | 7.78 | 1.79 |

*MELD* model for end-stage liver disease

* $p < 0.05$ across groups

[a] All remaining participants self-reported their gender as male

[b] Sustained virologic responder (SVR)

**Table 2** Means and standard deviations of the domain-level and global neurocognitive test composite *T* score change from baseline to follow-up

| Neurocognitive composite | Controls ($n$ = 22) | | SVRs[c] ($n$ = 57) | |
|---|---|---|---|---|
| | *M* | Std. error | *M* | Std. error |
| Attention[a] | | | | |
| *T* score change | 3.70 | 1.78 | 0.36 | 1.12 |
| Processing speed | | | | |
| *T* score change | 2.20 | 1.52 | 0.94 | 0.95 |
| Language | | | | |
| *T* score change | 0.68 | 3.13 | 1.22 | 3.87 |
| Learning and memory[a] | | | | |
| *T* score change | 4.98 | 2.06 | 2.08 | 1.29 |
| Executive function[a] | | | | |
| *T* score change | 2.30 | 1.70 | 1.03 | 1.07 |
| Motor | | | | |
| *T* score change | 2.05 | 2.34 | −0.22 | 1.47 |
| Global neurocognition[a] | | | | |
| *T* score change | 2.93[b] | 1.27 | 1.06 | 0.79 |

[a] Significantly better performance over time for all groups at the $p < 0.05$ level

[b] Significantly better performance over time than the other groups at the $p < 0.01$ level.

[c] Sustained virologic responder (SVR)

### Group differences in longitudinal white matter changes

We employed RMANOVA to determine whether longitudinal change in FA differed between the SVR and control groups (time ∗ group interaction). Results revealed significant interaction effects for posterior corona radiata FA, $F(1, 22) = 5.82$, $p = 0.03$, partial $\eta^2 = 0.21$, and superior longitudinal fasciculus FA, $F(1, 22) = 5.43$, $p = 0.03$, partial $\eta^2 = 0.20$, such that FA increased at a greater rate in the SVR group relative to the control group.

Regarding MD, there was a significant time ∗ group interaction effect found for fornix and stria terminalis, $F(1, 22) = 9.60$, $p = 0.01$, partial $\eta^2 = 0.32$, superior fronto-occipital fasciculus, $F(1, 22) = 10.01$, $p = 0.01$, partial $\eta^2 = 0.32$, splenium of the corpus callosum, $F(1, 22) = 7.67$, $p = 0.01$, partial $\eta^2 = 0.27$, and a trend towards an interaction effect for the superior corona radiata, $F(1, 22) = 4.06$, $p = 0.06$, partial $\eta^2 = 0.16$, and body of the corpus callosum MD, $F(1, 22) = 3.66$, $p = 0.07$, partial $\eta^2 = 0.25$. Specifically, the interaction effects revealed that SVRs demonstrated greater increases in MD over time compared to the control group. While none of the time ∗ group interaction effects for FA

withstood False Discovery Correction (FDR), the significant interaction effect on MD remained significant following FDR for the fornix and stria terminalis (FDR corrected $p$ value = 0.047), superior fronto-occipital fasciculus (FDR corrected $p$ value = 0.047), and splenium of the corpus callosum (FDR corrected $p$ value = 0.047).

### Group differences in longitudinal neuropsychological performance

Table 2 provides the means and standard deviations for the domain-level and global neurocognitive test composite $T$ score changes from baseline to follow-up, stratified by group. RMANOVA revealed a significant longitudinal time by group interaction for global neurocognitive performance $F(1, 77) = 5.99$, $p = 0.017$, partial $\eta^2 = 0.072$, and attention, $F(1, 77) = 4.78$, $p = 0.032$, partial $\eta^2 = 0.058$, indicating that the control group evidenced greater improvement over time in global cognition, driven by improvements in attention, than did the SVR group. The SVR group did not show any longitudinal cognitive improvements that were statistically greater than the control group. These significant interaction effects on cognition remained a statistical trend following FDR (FDR corrected $p$ value = 0.096).

Table 3 provides the results of correlations between absolute change (pre- to post-intervention) in cognitive domains

**Table 3** Correlations of absolute change of cognitive performance and change of fractional anisotropy values in sustained virologic responders

| | | Attention change | Processing speed change | Learning and memory change | Language change | Executive change | Motor change | Global change |
|---|---|---|---|---|---|---|---|---|
| ALIC FA change | Pearson correlation | 0.027 | 0.267 | 0.328 | 0.594* | 0.152 | 0.050 | 0.368 |
| | Significance | 0.928 | 0.357 | 0.253 | 0.032 | 0.603 | 0.865 | 0.216 |
| PLIC FA change | Pearson correlation | 0.197 | 0.131 | 0.353 | 0.600* | 0.595* | 0.044 | 0.583* |
| | Significance | 0.499 | 0.655 | 0.216 | 0.030 | 0.025 | 0.880 | 0.037 |
| PTR FA change | Pearson correlation | 0.090 | 0.079 | 0.122 | 0.466 | 0.224 | −0.143 | 0.243 |
| | Significance | 0.759 | 0.789 | 0.679 | 0.108 | 0.441 | 0.626 | 0.423 |
| ACR FA change | Pearson correlation | 0.122 | 0.425 | 0.139 | 0.347 | 0.093 | 0.180 | 0.178 |
| | Significance | 0.679 | 0.130 | 0.637 | 0.245 | 0.752 | 0.538 | 0.561 |
| SCR FA change | Pearson correlation | 0.284 | 0.369 | 0.236 | 0.351 | 0.274 | 0.135 | 0.325 |
| | Significance | 0.324 | 0.194 | 0.417 | 0.240 | 0.343 | 0.645 | 0.278 |
| PCR FA change | Pearson correlation | 0.316 | 0.256 | 0.205 | 0.372 | 0.174 | 0.028 | 0.315 |
| | Significance | 0.271 | 0.377 | 0.481 | 0.210 | 0.553 | 0.923 | 0.294 |
| FX ST FA change | Pearson correlation | −0.161 | 0.182 | 0.491 | 0.728** | 0.210 | 0.249 | 0.504 |
| | Significance | 0.582 | 0.533 | 0.075 | 0.005 | 0.471 | 0.390 | 0.079 |
| SLF FA change | Pearson correlation | 0.302 | 0.124 | −0.009 | 0.272 | 0.298 | −0.050 | 0.191 |
| | Significance | 0.294 | 0.672 | 0.975 | 0.369 | 0.301 | 0.866 | 0.533 |
| SFO FA change | Pearson correlation | 0.276 | 0.521 | 0.690** | 0.341 | 0.191 | 0.191 | 0.519 |
| | Significance | 0.339 | 0.056 | 0.006 | 0.255 | 0.513 | 0.514 | 0.069 |
| IFO FA change | Pearson correlation | −0.076 | 0.186 | 0.129 | 0.659* | 0.049 | 0.010 | 0.259 |
| | Significance | 0.796 | 0.524 | 0.660 | 0.014 | 0.869 | 0.972 | 0.393 |
| GCC FA change | Pearson correlation | 0.166 | 0.327 | 0.041 | −0.270 | −0.147 | 0.226 | −0.135 |
| | Significance | 0.571 | 0.254 | 0.890 | 0.373 | 0.615 | 0.437 | 0.661 |
| BCC FA change | Pearson correlation | −0.084 | 0.214 | 0.622* | 0.634* | 0.399 | 0.200 | 0.543 |
| | Significance | 0.776 | 0.463 | 0.018 | 0.020 | 0.158 | 0.493 | 0.055 |
| SCC FA change | Pearson correlation | −0.148 | 0.208 | 0.459 | 0.327 | 0.564* | 0.008 | 0.317 |
| | Significance | 0.613 | 0.476 | 0.098 | 0.275 | 0.036 | 0.979 | 0.291 |
| RLIC FA change | Pearson correlation | 0.101 | 0.033 | 0.121 | 0.451 | 0.236 | 0.098 | 0.325 |
| | Significance | 0.732 | 0.912 | 0.681 | 0.122 | 0.418 | 0.740 | 0.278 |

*FA* fractional anisotropy, *ACR* anterior corona radiata, *ALIC* anterior limb of the internal capsule, *BCC* body of the corpus callosum, *FX ST* fornix/stria terminalis, *GCC* genu of the corpus callosum, *IFO* inferior frontal-occipital fasciculus, *PCR* posterior corona radiata, *PLIC* posterior limb of the internal capsule, *PTR* posterior thalamic radiations, *RLIC* retrolenticular part of the internal capsule, *SCC* splenium of the corpus callosum, *SCR* superior corona radiata, *SFO* superior frontal-occipital fasciculus, *SLF* superior longitudinal fasciculus

*Significant at the $p<0.05$ level; ** Significant at the $p<0.01$ level

and change in FA values. Longitudinal increases in FA were significantly correlated with longitudinal improvement in language (anterior limb internal capsule, posterior limb internal capsule, fornix, superior fronto-occipital fasciculus, inferior fronto-occipital fasciculus, body of the corpus callosum), learning and memory (superior fronto-occipital fasciculus, body of corpus callosum, trend fornix/splenium of corpus callosum), executive function (posterior limb internal capsule), processing speed (trend posterior thalamic radiation/superior fronto-occipital fasciculus) and global neurocognitive functioning (posterior limb internal capsule, body of corpus callosum, trend superior fronto-occipital fasciculus/fornix).

Table 4 provides the results of correlations between absolute change (pre- to post-intervention) in cognitive domains and change in MD values. Longitudinal decreases in MD were significantly correlated with longitudinal improvement in language (anterior corona radiata, superior corona radiata, fornix, genu of corpus callosum, trend posterior limb internal capsule/body of corpus callosum), learning and memory (posterior thalamic radiation, body of corpus callosum, trend superior corona radiata), executive function (posterior limb internal capsule, body of corpus callosum, trend superior corona radiata), processing speed (posterior thalamic radiation, trend superior fronto-occipital fasciculus), motor (anterior corona radiata, trend retrolenticular portion internal capsule) and global cognitive functioning (posterior limb internal capsule, superior corona radiata, fornix, retrolenticular portion internal capsule, trend anterior corona radiata).

**Table 4** Correlations of absolute change of cognitive performance and change of mean diffusivity values in sustained virologic responders

| | | Attention change | Processing speed change | Learning and memory change | Language change | Executive change | Motor change | Global change |
|---|---|---|---|---|---|---|---|---|
| ALIC MD change | Pearson correlation | −0.226 | −0.271 | −0.039 | −0.296 | −0.245 | −0.267 | −0.417 |
| | Significance | 0.457 | 0.370 | 0.900 | 0.349 | 0.421 | 0.378 | 0.177 |
| PLIC MD change | Pearson correlation | −0.218 | 0.054 | −0.393 | −0.512 | −0.568* | −0.445 | −0.656* |
| | Significance | 0.473 | 0.861 | 0.184 | 0.089 | 0.043 | 0.128 | 0.021 |
| PTR MD change | Pearson correlation | −0.059 | 0.679* | −0.587* | −0.261 | −0.435 | −0.434 | −0.425 |
| | Significance | 0.849 | 0.011 | 0.035 | 0.412 | 0.137 | 0.139 | 0.168 |
| ACR MD change | Pearson correlation | −0.044 | 0.076 | −0.430 | −0.693* | 0.015 | −0.579* | −0.534 |
| | Significance | 0.885 | 0.805 | 0.142 | 0.012 | 0.960 | 0.038 | 0.074 |
| SCR MD change | Pearson correlation | −0.348 | −0.083 | −0.537 | −0.644* | −0.528 | −0.438 | −0.820** |
| | Significance | 0.244 | 0.788 | 0.058 | 0.024 | 0.064 | 0.134 | 0.001 |
| PCR MD change | Pearson correlation | −0.277 | 0.121 | −0.198 | 0.031 | −0.301 | −0.409 | −0.277 |
| | Significance | 0.360 | 0.695 | 0.517 | 0.925 | 0.318 | 0.165 | 0.383 |
| FX ST MD change | Pearson correlation | 0.149 | −0.140 | −0.434 | −0.701* | −0.183 | −0.460 | −0.579* |
| | Significance | 0.627 | 0.647 | 0.138 | 0.011 | 0.549 | 0.114 | 0.049 |
| SLF MD change | Pearson correlation | −0.354 | −0.359 | 0.157 | −0.200 | 0.205 | −0.445 | −0.246 |
| | Significance | 0.235 | 0.228 | 0.609 | 0.532 | 0.502 | 0.128 | 0.442 |
| SFO MD change | Pearson correlation | 0.155 | −0.486 | −0.336 | −0.002 | 0.310 | −0.150 | 0.079 |
| | Significance | 0.613 | 0.092 | 0.262 | 0.994 | 0.302 | 0.625 | 0.808 |
| IFO MD change | Pearson correlation | 0.292 | −0.297 | 0.452 | 0.032 | 0.265 | −0.140 | 0.252 |
| | Significance | 0.333 | 0.325 | 0.121 | 0.921 | 0.382 | 0.649 | 0.429 |
| GCC MD change | Pearson correlation | −0.025 | −0.318 | −0.190 | −0.678* | −0.406 | −0.060 | −0.472 |
| | Significance | 0.935 | 0.290 | 0.534 | 0.015 | 0.169 | 0.845 | 0.121 |
| BCC MD change | Pearson correlation | 0.271 | −0.049 | −0.553 | −0.525 | −0.543 | −0.197 | −0.465 |
| | Significance | 0.371 | 0.874 | 0.050 | 0.080 | 0.055 | 0.520 | 0.128 |
| SCC MD change | Pearson correlation | 0.357 | −0.266 | −0.091 | −0.065 | −0.109 | 0.166 | −0.026 |
| | Significance | 0.231 | 0.379 | 0.768 | 0.842 | 0.723 | 0.588 | 0.936 |
| RLIC MD change | Pearson correlation | −0.487 | 0.185 | −0.389 | −0.375 | −0.607* | −0.494 | −0.702* |
| | Significance | 0.092 | 0.546 | 0.189 | 0.230 | 0.028 | 0.086 | 0.011 |

*MD* mean diffusivity, *ACR* anterior corona radiata, *ALIC* anterior limb of the internal capsule, *BCC* body of the corpus callosum, *FX ST* fornix/stria terminalis, *GCC* genu of the corpus callosum, *IFO* inferior frontal-occipital fasciculus, *PCR* posterior corona radiata, *PLIC* posterior limb of the internal capsule, *PTR* posterior thalamic radiations, *RLIC* retrolenticular part of the internal capsule, *SCC* splenium of the corpus callosum, *SCR* superior corona radiata, *SFO* superior frontal-occipital fasciculus, *SLF* superior longitudinal fasciculus

*Significant at the $p<0.05$ level; **Significant at the $p<0.01$ level

### Longitudinal relationship between change in cognition and white matter integrity in SVRs

RMANOVAs compared changes in DTI parameters between HCV SVRs who experienced improved global neuropsychological performance (again, defined by cognitive improvement in excess of the control group's mean change plus 0.5 SD), versus those SVR participants who did not demonstrate that degree of improvement. Results revealed significant group x time interaction effects for FA changes in several regions including the posterior limb of the internal capsule, $F(1, 12) = 5.05$, $p = 0.050$, partial $\eta^2 = 0.39$, fornix, $F(1, 12) = 5.22$, $p = 0.049$, partial $\eta^2 = 0.40$, and body of the corpus callosum, $F(1, 12) = 6.98$, $p = 0.030$, partial $\eta^2 = 0.47$. Specifically, SVRs whose neuropsychological performance improved demonstrated positive absolute FA change scores, whereas those who did not improve cognitively demonstrated negative FA absolute change, indicating that improvements in neurocognition were associated with increases in white matter integrity. There was also a trend towards a significant interaction effect in the splenium of the corpus callosum FA, $F(1, 12) = 4.44$, $p = 0.068$, partial $\eta^2 = 0.36$, such that cognitively improved SVRs displayed increased FA compared to those who did not improve cognitively (Table 5).

With regard to MD changes, there was a significant group × time interaction effect in the posterior limb of the internal capsule, $F(1, 12) = 7.43$, $p = 0.026$, partial $\eta^2 = 0.48$, such that the cognitively improved group evidenced decreasing MD (i.e., more intact white matter over time) whereas the cognitively stable group evidenced increasing MD over time. Further, there were significant interaction effects in MD of the posterior thalamic radiation, $F(1, 12) = 7.84$, $p = 0.023$, partial $\eta^2 = 0.50$, fornix, $F(1, 12) = 6.06$, $p = 0.039$, partial $\eta^2 = 0.43$, and body of the corpus callosum, $F(1, 12) = 6.01$, $p = 0.008$, partial $\eta^2 = 0.61$, such that MD increased in the cognitively stable group (i.e., decrease in white matter integrity) but remained stable in the cognitively improved groups (Table 6).

## Discussion

The current study examined the longitudinal effects of PEG-IFN/RBV treatment and clearance of HCV infection on neuropsychological performance and microstructural brain abnormalities. Contrary to expectation, our group-level longitudinal analyses did not reveal significant improvement in neurocognitive performance in the SVR group compared to the control group. However, there was a subgroup of SVR participants who did demonstrate a significant improvement in cognition relative to controls. Importantly, analysis of DTI data did reveal beneficial effects associated with clearing the virus particularly in the posterior corona radiata and the superior longitudinal fasciculus.

Indeed, DTI metrics of white matter integrity were more sensitive markers of improvement related to clearing HCV than was neuropsychological testing. Although the SVR group did not demonstrate cognitive improvement beyond that of the control group, improvement in global and domain-level cognitive performance was related to improved white matter integrity (i.e., increased FA, reduced MD). Further, within the SVR participants who demonstrated clinically significant improvement in overall neuropsychological performance, we found that they evidenced even better DTI metrics/white matter integrity in multiple regions. These improvements in brain integrity within a subset of the SVRs may well be attributable to HCV clearance and may suggest that these individuals will continue to improve over time. Given that there is likely to be inter-individual differences in the timetable for recovery from HCV effects, as well as the adverse effects of interferon, it is possible that more participants will demonstrate improved brain integrity and associated improvements in neurocognition as time ensues. An additional follow-up evaluation within this cohort would provide the data necessary to address these clinically valuable questions.

Further, DTI analysis found that the SVR group displayed longitudinal increases in FA in the posterior corona radiata and superior longitudinal fasciculus compared to the control

**Table 5** Results of RMANOVAs for change in fractional anisotropy in cognitively stable and improved hepatitis C participants with a sustained virologic response

| Region | Group | FA change | *F* | *p* | Partial $\eta^2$ |
|---|---|---|---|---|---|
| Posterior limb internal capsule | Cog. improved | 0.027 (0.026) | 5.05 | .05 | 0.39 |
| | Not improved | −0.001 (0.011) | | | |
| Body of Corpus callosum | Cog. improved | 0.015 (0.030) | 6.98 | .030 | 0.47 |
| | Not improved | −0.026 (0.017) | | | |
| Fornix and stria terminalis | Cog. improved | 0.006 (0.017) | 5.22 | .049 | 0.40 |
| | Not improved | −0.030 (0.031) | | | |
| Splenium of corpus callosum | Cog. improved | 0.007 (0.018) | 4.44 | .068 | 0.36 |
| | Not improved | −0.013 (0.007) | | | |

*FA* fractional anisotropy

Cog. improved global neuropsychological composite *T* score change ≥ mean + 0.5 *SD*

Not improved global neuropsychological composite *T* score change < mean + 0.5 *SD*

**Table 6** Results of RMANOVAs for change in mean diffusivity in cognitively stable and improved hepatitis C participants with a sustained virologic response

| Region | Group | MD change | *F* | *p* | Partial $\eta^2$ |
|---|---|---|---|---|---|
| Posterior limb internal capsule | Cog. improved | −5.7E−5 (9.9E−5) | 7.43 | .026 | 0.48 |
| | Not improved | 1.4E−4 (1.3E−4) | | | |
| Posterior thalamic radiation | Cog. improved | 2.6E−5 (7.0E−5) | 7.84 | .023 | 0.50 |
| | Not improved | 1.4E−4 (2.4E−5) | | | |
| Fornix and stria terminalis | Cog. improved | 4.5E−5 (9.5E−5) | 6.06 | .039 | 0.43 |
| | Not improved | 2.9E−4 (2.1E−4) | | | |
| Body of corpus callosum | Cog. improved | 4.0E−6 (2.0E−4) | 6.01 | .008 | 0.61 |
| | Not improved | 3.8E−4 (2.7E−4) | | | |

*MD* mean diffusivity

Cog. improved global neuropsychological composite *T* score change ≥ mean + 0.5 *SD*

Not improved global neuropsychological composite *T* score change < mean + 0.5 *SD*

group, indicating that clearance of the virus was associated with improved white matter integrity in these regions. However, the SVR group also demonstrated longitudinally increased MD in the fornix and stria terminalis, splenium of the corpus callosum, and superior fronto-occipital fasciculus. Increased MD is generally indicative of reduced white matter integrity and can be used to differentiate lesion types. For example, in herpes simplex encephalitis, increased MD that remained elevated over time has been associated with severe, possibly irreversible damage (e.g., gliosis), whereas increased MD which normalized over time following successful eradication of the herpes simplex virus was associated with edema and demyelination (Sämann et al. 2003). Within our sample, increased MD at baseline was found in the superior fronto-occipital fasciculus, which remained elevated over time, and in the external capsule, which normalized over time. Therefore, our MD results demonstrate regionally specific severity of inflammatory tissue damage which may be the result of HCV and/or the effects of interferon. Although FA revealed regions of improved neurointegrity, MD results indicated that white matter damage remained even after successful eradication of the virus. It is possible that the subgroup that improved had less inflammation prior to beginning treatment or reduced the level of inflammation to a greater degree post-treatment than did the group that did not display cognitive improvement. Importantly, both groups received the same number of treatments across the same number of weeks, though exact treatment dose varied by individual.

Virologic factors which could result in increased MD include glial activation and inflammation (Cloak et al. 2004), CNS cytokine responses (Raison et al. 2010), and HCV-associated apoptosis (Shibata et al. 1994). This finding may also account for the absence of a strong relationship between HCV clearance and improved neuropsychological performance. It is also possible that testing patients 12 weeks after cessation of interferon was not far enough out in time from treatment to detect improvement in neurocognition and/or neuroanatomy related to clearing HCV. In one study in which follow-up was conducted 48 weeks after treatment cessation, significant improvement in areas of attention and working memory was found in those HCV patients who successfully cleared the virus, suggesting that this longer timeframe was sufficient to allow reversal of the causative neurotoxic factors (Bladowska et al. 2013a). It is therefore possible that over time additional benefit of HCV clearance would become yet more pronounced.

There are limitations to the current study. First, while the aim of this study was to investigate the neurocognitive and neuroanatomic sequelae of successful HCV eradication, the HCV treatment (PEG-IFN/RBV) used in this study has largely been replaced by newer medications, in part due to the neurotoxic effects of PEG-IFN/RBV. Therefore, as previously discussed, it is possible that our results were somewhat influenced by deleterious side effects of PEG-IFN. While, for this very reason, the follow-up assessment was not conducted until 12 weeks after discontinuation of interferon, it is possible that those adverse side effects may persist beyond 12 weeks. Nevertheless, it is important to note that results demonstrated improved white matter integrity and associated improvements in cognitive performance attributable to SVR, even in the context of potential treatment-related toxicity. Future studies may further our understanding of the neurocognitive and neuroanatomic effects of SVR following newer interferon-sparing HCV treatment regimens. Next, while we attempted to control for numerous demographic variables, there remain many psychosocial differences between our patient groups which can account for some portion of the variance in neuropsychological performance and brain microstructure reported herein. One such factor is historical drug use, which we were unable to control for between groups as data on drug use history was not collected for the control group. While urinalysis toxicology was used to exclude potential participants with current illicit substance use, past cocaine or opiate use was reported in 52% of patients with HCV diagnosis. Although post-hoc analyses did not find significant differences in baseline neuropsychological performance or neuroimaging data between HCV patients with and without self-reported past history of substance abuse, residual effects of previous drug use on

neurologic functioning cannot be ruled out. Finally, our sample size was limited by attrition, which was a notable methodologic concern given that patients may choose to discontinue treatment for a variety of reasons, including unpleasantness of taking the medication and severity of side effects.

## Conclusions

Overall, this study provides initial evidence that a subgroup of HCV+ patients experience improvements in cognitive functioning associated with a SVR. Furthermore, improvements in cognitive functioning in this group appear related to positive changes in white matter integrity.

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**Compliance with ethical standards** All procedures were approved by the University of California, Los Angeles and VA Greater Los Angeles Healthcare System Institutional Review Boards. All participants provided written informed consent prior to entering the study.

**Conflict of interest** The authors declare that they have no conflict of interest.

## References

Benedict RH (1997) Brief visuospatial memory test—revised. Psychological Assessment Resources, Odessa (Florida)

Benton AL, Hamsher KS, Sivan AB (1994) Multilingual aphasia examination (MAE), 3rd edn. Psychological Assessment Resources, Odessa (Florida)

Bladowska J, Zimny A, Kołtowska A, Szewczyk P, Knysz B, Gąsiorowski J et al (2013a) Evaluation of metabolic changes within the normal appearing gray and white matters in neurologically asymptomatic HIV-1-positive and HCV-positive patients: magnetic resonance spectroscopy and immunologic correlation. Eur J Radiol 82:686–692

Bladowska J, Zimny A, Knysz B, Małyszczak K, Kołtowska A, Szewczyk P et al (2013b) Evaluation of early cerebral metabolic, perfusion and microstructural changes in HCV-positive patients: a pilot study. J Hepatol 59:651–657

Byrnes V, Miller A, Lowry D, Hill E, Weinstein C, Alsop D et al (2012) Effects of anti-viral therapy and HCV clearance on cerebral metabolism and cognition. J Hepatol 56:549–556

Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I et al (2004) Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. J Clin Exp Neuropsychol 26:307–319

Cherner M, Letendre S, Heaton RK, Durelle J, Marquie-Beck J, Gragg B et al (2005) Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. Neurology 64:1343–1347

Clifford DB, Smurzynski M, Park LS, Yeh T-M, Zhao Y, Blair L et al (2009) Effects of active HCV replication on neurologic status in HIV RNA virally suppressed patients. Neurology 73:309–314

Cloak CC, Chang L, Ernst T (2004) Increased frontal white matter diffusion is associated with glial metabolites and psychomotor slowing in HIV. J Neuroimmunol 157:147–152

Córdoba J, Flavià M, Jacas C, Sauleda S, Esteban JI, Vargas V et al (2003) Quality of life and cognitive function in hepatitis C at different stages of liver disease. J Hepatol 39:231–238

Forton D, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J et al (2002) Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. Hepatology 35:433–439

Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC (2004) Identification of unique hepatitis C virus quasispecies in the central nervous system and comparative analysis of internal translational efficiency of brain, liver, and serum variants. J Virol 78:5170–5183

Forton DM, Taylor-Robinson SD, Thomas HC (2006) Central nervous system changes in hepatitis C virus infection. Eur J Gastroenterol Hepatol 18:333–338

Gaeta L, Di Palo M, Fasanaro AM, Loguercio C (2013) Cognitive dysfunctions in hepatitis C virus (HCV) infection. A mini review. Curr Neurobiol 4:43–46

Gronwall DMA (1977) Paced auditory serial-addition task: a measure of recovery from concussion. Percept Mot Skills 44:367–373

Grover VP, Pavese N, Koh SB, Wylezinska M, Saxby BK, Gerhard A et al (2012) Cerebral microglial activation in patients with hepatitis C: in vivo evidence of neuroinflammation. J Viral Hepat 19:89–96

Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL et al (2008) Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology 48:169–176

Hilsabeck RC, Hassanein TI, Carlson MD, Ziegler EA, Perry W (2003) Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C. J Int Neuropsychol Soc 9:847–854

Hinkin CH, Castellon SA, Levine AJ, Barclay TR, Singer EJ (2008) Neurocognition in individuals co-infected with HIV and hepatitis C. J Addict Dis 27:11–17

Huckans M, Fuller B, Wheaton V, Jaehnert S, Ellis C, Kolessar M, & Sasaki AW (2015) A longitudinal study evaluating the effects of interferon-alpha therapy on cognitive and psychiatric function in adults with chronic hepatitis C. J Psychosom Res 78(2):184–192

Juengling FD, Ebert D, Gut O, Engelbrecht MA, Rasenack J, Nitzsche EU et al (2000) Prefrontal cortical hypometabolism during low-dose interferon alpha treatment. Psychopharmacology 152:383–389

Kløve H (1963) Grooved pegboard. Lafayette Instruments, Lafayette (Indiana)

Kraus MR, Schäfer A, Teuber G, Porst H, Sprinzl K, Wollschläger S et al (2013) Improvement of neurocognitive function in responders to an antiviral therapy for chronic hepatitis C. Hepatology 58:497–504

Laskus T, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M et al (2002) Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. J Virol 76:10064–10068

Letendre S, Paulino AD, Rockenstein E, Adame A, Crews L, Cherner M et al (2007) Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV. J Infect Dis 196:361–370

Lowry D, Burke T, Galvin Z, Ryan JD, Russell J, Murphy A et al (2016) Is psychosocial and cognitive dysfunction misattributed to the virus in hepatitis C infection? Select psychosocial contributors identified. J Viral Hepat 23:584–595

McAndrews MP, Farcnik K, Carlen P, Damyanovich A, Mrkonjic M, Jones S et al (2005) Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors. Hepatology 41:801–808

Nuechterlein KH, Green MF, Kern RS, Baade LE, Barch DM, Cohen JD et al (2008) The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. Am J Psychiatry 165:203–213

Posada C, Morgan EE, Moore DJ, Woods SP, Letendre SL, Grant I et al (2009) Neurocognitive effects of the hepatitis C virus. Curr Hepat Rep 8(S1):18–26

Price RW, Yiannoutsos CT, Clifford DB, Zaborski L, Tselis A, Sidtis JJ et al (1999) Neurological outcomes in late HIV infection: adverse impact of neurological impairment on survival and protective effect of antiviral therapy. AIDS 13:1677–1685

Raison CL, Dantzer R, Kelley KW, Lawson MA, Woolwine BJ, Vogt G et al (2010) CSF concentrations of brain tryptophan and kynurenines during immune stimulation with IFN-α: relationship to CNS immune responses and depression. Mol Psychiatry 15:393–403

Reitan RM (1958) Trail making test: manual for administration, scoring and interpretation. Department of Neurology, Section of Neuropsychology, Indiana University Medical Center, Indianapolis

Sämann PG, Schlegel J, Müller G, Prantl F, Emminger C, Auer DP (2003) Serial proton MR spectroscopy and diffusion imaging findings in HIV-related herpes simplex encephalitis. Am J Neuroradiol 24: 2015–2019

Shapiro AM, Benedict RHB, Schretlen D, Brandt J (1999) Construct and concurrent validity of the Hopkins verbal learning test—revised. Clin Neuropsychol 13:348–358

Shawcross D, Jalan R (2005) The pathophysiologic basis of hepatic encephalopathy: central role for ammonia and inflammation. Cell Mol Life Sci 62:2295–2304

Shibata S, Kyuwa S, Lee SK, Toyoda Y, Goto N (1994) Apoptosis induced in mouse hepatitis virus-infected cells by a virus-specific CD8+ cytotoxic T-lymphocyte clone. J Virol 68:7540–7545

Soogoor M, Lynn HS, Donfield SM, Gomperts E, Bell TS, Daar ES et al (2006) Hepatitis C virus infection and neurocognitive function. Neurology 67:1482–1485

Stroop JR (1935) Studies of interference in serial verbal reactions. J Exp Psychol 18:643–662

Thein H, Maruff P, Krahn M, Kaldor J, Koorey D, Brew B et al (2007) Improved cognitive function as a consequence of hepatitis C virus treatment. HIV Med 8:520–528

Tully DC, Hjerrild S, Leutscher PD, Renvillard SG, Ogilvie CB, Bean DJ et al (2016) Deep sequencing of hepatitis C virus reveals genetic compartmentalization in cerebrospinal fluid from cognitively impaired patients. Liver Int 36:1418–1424

Wechsler D (1997) Wechsler adult intelligence scale, 3rd edn. The Psychological Corporation, San Antonio

Weissenborn K, Krause J, Bokemeyer M, Hecker H, Schüler A, Ennen JC et al (2004) Hepatitis C virus infection affects the brain—evidence from psychometric studies and magnetic resonance spectroscopy. J Hepatol 41:845–851

Zeuzem S (2008) Interferon-based therapy for chronic hepatitis C: current and future perspectives. Nat Clin Pract Gastroenterol Hepatol 5: 610–622