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Journal

Journal of NeuroVirology, 20(6)

ISSN

1355-0284

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Publication Date

2014-12-01

DOI

10.1007/s13365-014-0265-3

Peer reviewed

# Persistent neurocognitive decline in a clinic sample of hepatitis C virus-infected persons receiving interferon and ribavirin treatment

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Received: 11 February 2014 / Revised: 31 May 2014 / Accepted: 12 June 2014 / Published online: 18 October 2014  
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**Abstract** Treatment of hepatitis C virus (HCV) with pegylated interferon and ribavirin (IFN/RBV) can be associated with neuropsychiatric side effects, which may necessitate dose reductions or treatment discontinuation. This study aimed to characterize the time course and predictors of cognitive and affective/mood symptoms after IFN/RBV treatment initiation. Forty individuals enrolled in a longitudinal project underwent comprehensive cognitive, medical, and psychiatric assessment at baseline and 10 weeks, 6 months, 12 months, and 18 months after treatment initiation. Analyses were conducted to determine the prevalence of neurocognitive impairment over time; explicate the relationship between neurocognitive impairment, neuropsychiatric symptoms, and liver disease at each time point; and identify predictors of neurocognitive decline as well as cognitive effects of viral clearance. By 10 weeks after initiating IFN/RBV, the prevalence of neurocognitive

impairment rose from 22.5 to 47.4 % ( $p < 0.05$ ). Infection with genotype 1 and premonitory depression were associated with more severe declines ( $p < 0.05$ ). After 18 months, 42.5 % remained neurocognitively impaired, independent of viral clearance, severity of liver disease, and current depressive symptoms. Undetectable viral load was not associated with improvement 18 months after initiating treatment ( $p > 0.10$ ). Results of the current study indicate that IFN/RBV treatment-emergent neurocognitive declines are significant, prevalent, and may persist long after treatment cessation. Clinicians should monitor cognition throughout the course of treatment for HCV, noting that early declines may indicate individuals at elevated risk for persistent neurocognitive impairment. Longer-term studies are needed to determine whether lasting declines may remit over longer intervals or with newer direct acting agents.

**Keywords** Antiviral treatment · Side effects (treatment) · Neuropsychological effects · Cognitive dysfunction/impairment · Depressive symptoms

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## Abbreviation

|         |                                    |
|---------|------------------------------------|
| HCV     | Hepatitis C virus                  |
| IFN/RBV | Interferon and ribavirin           |
| CNS     | Central nervous system             |
| NIDA    | National Institute on Drug Abuse   |
| UCSD    | University of California San Diego |
| IgG     | Immunoglobulin G                   |
| ELISA   | Enzyme-linked immunosorbent assay  |
| HIV     | Human immunodeficiency virus       |
| MDD     | Major depressive disorder          |
| GDS     | Global deficit score               |
| SD      | Standard deviation                 |
| BDI-II  | Beck Depression Inventory-II       |

APRI Aspartate aminotransferase to platelet ratio index

## Introduction

Hepatitis C virus (HCV) primarily infects hepatocytes and may result in inflammation, fibrosis, cirrhosis, and hepatocellular carcinoma. However, HCV also causes extrahepatic disease (Sene et al. 2004) impacting numerous organ systems (e.g., endocrine, lymphatic, renal) including central nervous system (CNS) structure and function (Laskus et al. 2005; Wilkinson et al. 2009; Murray et al. 2008; Vargas et al. 2002; Schaefer et al. 2012). Whether CNS disturbances are due to primary neurotoxic effects of the virus, secondary effects of immune/glial activation and liver disease (Senzolo et al. 2011), or both, they are of sufficient magnitude to increase disease burden and impact patient management (Russo and Fried 2003). Many individuals with HCV report cognitive symptoms, which are often associated with objective evidence of neurocognitive impairment (Forton et al. 2005; Weissenborn et al. 2004; Hilsabeck et al. 2002) as well as psychiatric syndromes (Schaefer et al. 2012). These sequelae occur commonly, are often present prior to the development of clinically significant liver disease, and may be exacerbated by advanced liver disease and other common comorbidities (Pattullo et al. 2011; Córdoba et al. 2003). Although combination treatment with pegylated interferon and ribavirin (IFN/RBV) can result in viral eradication in over 50 % of individuals who begin treatment (McNutt et al. 2012), this regimen is associated with numerous adverse effects of its own. Perhaps most notably, IFN/RBV is associated with prominent cognitive and neuropsychiatric effects (Raison et al. 2009), which are reported in up to 80 % of patients after beginning treatment, and often necessitate dose reductions (40 % of treated patients) or discontinuation of therapy (20 % of treated patients) (McNutt et al. 2012; Fontana 2000; Valentine and Meyers 2005; Schaefer et al. 2002; de Knecht et al. 2011). Due to inconsistencies in the methodologies of existing studies, the predictors and long-term effects of these neurocognitive and neuropsychiatric complications are largely unknown. This is particularly the case in individuals with multiple risk factors for cognitive impairment and psychiatric symptomatology, as these are exclusion criteria in many treatment studies (Schmidt et al. 2009).

At present, IFN/RBV remains in widespread use despite a relatively high prevalence of treatment-related complications, although IFN-sparing regimens are becoming available. Some side effects (e.g., flu-like symptoms) appear to be dose-dependent and reversible upon cessation of IFN/RBV therapy (Russo and Fried 2003; Neri et al. 2010), while others (e.g., fatigue, mood changes, and cognitive impairment) may have a more insidious onset and more variable course (Reichenberg et al. 2005). For example, evidence suggests that depression,

anxiety, neurovegetative symptoms, and cognitive dysfunction can increase within 2 weeks of initiating treatment, exhibiting a fluctuating and worsening course thereafter (Dusheiko 1997; Reichenberg et al. 2005). In turn, IFN-induced depression may reduce treatment efficacy by decreasing responsiveness to anti-retroviral treatment. There is mixed evidence as to whether neuropsychiatric symptoms may resolve following treatment cessation (McNutt et al. 2012; Schmidt et al. 2009; Thein et al. 2007; McAndrews et al. 2005). In some studies, persistent depressive symptoms and cognitive disturbances have been detected after as long as 72 weeks even without premorbid risks, suggesting that it may be beneficial to monitor patients even after discontinuation of treatment, particularly in the presence of independent neurocognitive or neuropsychiatric risk factors (Reichenberg et al. 2005). However, precisely which factors may confer additional risk for incident or lasting neurocognitive and neuropsychiatric symptoms has not been well established. Identifying these relative risks and understanding their implications are critical, as a disproportionate number of HCV-infected individuals have multiple conditions (e.g., substance abuse, depression) that may produce or exacerbate neurocognitive impairment and mood disturbances, which in turn may contribute to functional disability and worse health-related quality of life.

Published studies on IFN/RBV vary in their patient characteristics, control groups, methodology (e.g., time points and duration of follow-up), cognitive assessments, and consideration of potentially confounding factors such as liver disease, medical comorbidity, premorbid depression, and substance abuse/dependence (Valentine and Meyers 2005; Hilsabeck et al. 2002; McAndrews et al. 2005). In particular, many studies examine only patients within a narrow range of mild or severe liver disease, further clouding interpretation of relationships along a continuum of hepatic disease. For this reason, the current observational study endeavored to (1) determine the neurocognitive correlates of IFN/RBV treatment in a group of individuals inclusive of comorbidities commonly seen in HCV-infected persons (e.g., histories of depression and substance abuse disorders and a range of medical and psychological health at pretreatment baseline), and if possible, to (2) identify predictors of decline and deficits in neurocognitive and neuropsychiatric functioning from among relevant clinical variables (e.g., failure to achieve sustained viral clearance, liver fibrosis stage).

## Participants and methods

### Participants

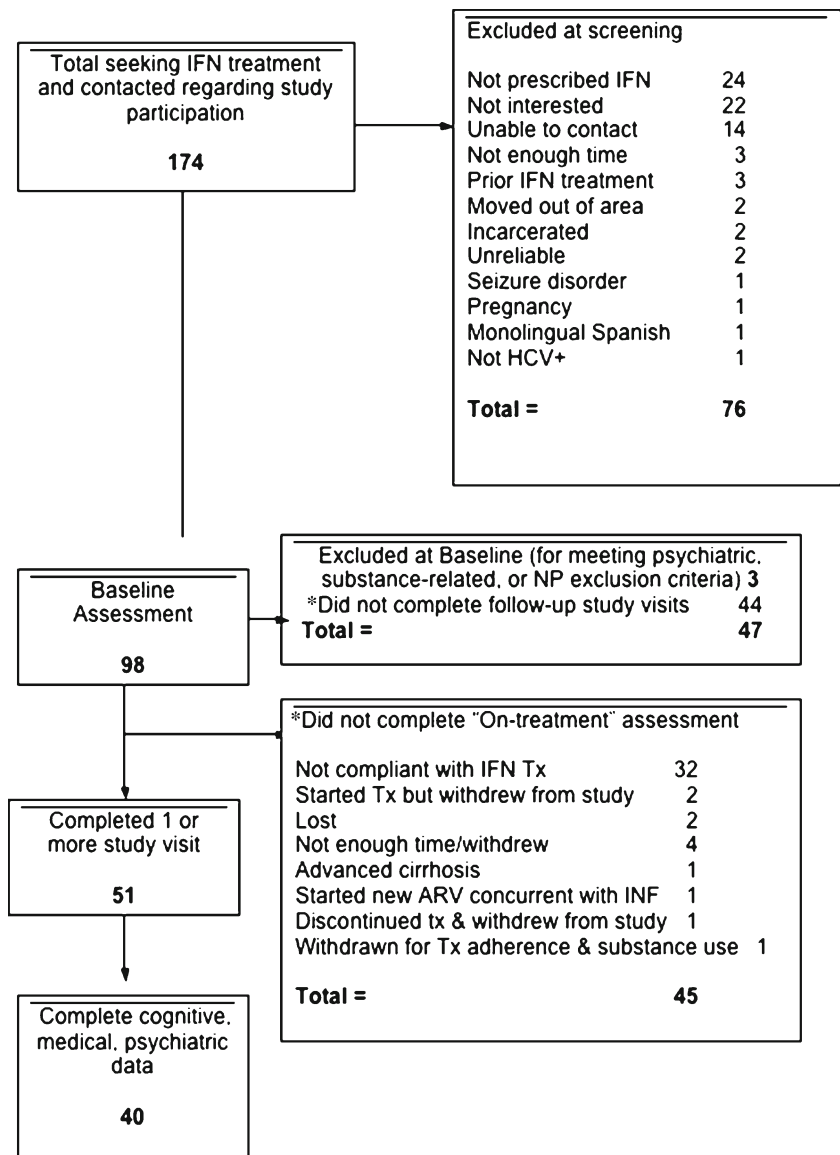
All participants were enrolled in a longitudinal National Institute on Drug Abuse (NIDA)-funded study at the University of California San Diego (UCSD) examining the neuropsychiatric effects of antiviral treatment for HCV disease. A total of 174 individuals were screened for eligibility

for this observational substudy (see flow chart depicting enrollment and selection of participants in Fig. 1). Participants were selected if they met the following criteria: (1) were prescribed IFN/RBV and scheduled to receive care at the UCSD Hepatology Clinic, (2) had never received IFN therapy at the time of initial assessment, and (3) were available and interested in completing additional assessments at designated time points. Informed consent was obtained from each participant, and the study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki by obtaining a priori approval by the UCSD Human Research Protection Program. HCV diagnoses were confirmed through detection of HCV immunoglobulin G (IgG) antibody in plasma by enzyme-linked immunosorbent assay. HCV RNA was quantified by real-time polymerase chain reaction (PCR), and HCV genotyping was performed by a commercial lab. Liver

biopsies were administered as clinically warranted (results available for 35 of the 40 participants) (see Table 1 for HCV and fibrosis characteristics of the sample at baseline).

Exclusion criteria included inability to provide informed consent, history of severe psychiatric (e.g., psychosis) or neurological (e.g., seizures) disorders, and active substance use. Our sample included conditions that are commonly associated with HCV. Specifically, seven individuals tested positive for human immunodeficiency virus (HIV), and as HIV is another common comorbidity of HCV disease, HIV-infected subjects were included in the analysis after confirming that their demographic, psychiatric, liver fibrosis, and HCV disease characteristics did not significantly differ from HIV-participants at baseline. Demographic, HCV, HIV, psychiatric, and neuropsychological characteristics for this sample are summarized in Table 2.

**Fig. 1** Study recruitment, screening, and enrollment



**Table 1** Demographic, psychiatric, and substance use characteristics ( $n=40$ )

|   |             |
|---|-------------|
| Demographics                                |             |
| Age (years) mean (SD)                       | 47.8 (8.5)  |
| Education (years) a mean (SD)               | 12.9 (2.0)  |
| Sex +                                       | 20 (50.0)   |
| Caucasian +                                 | 28 (70.0)   |
| African-American                            | 3 (7.5)     |
| Hispanic                                    | 8 (20.0)    |
| Other                                       | 1 (2.5)     |
| Reading literacy (WRAT3), mean (SD)         | 96.0 (12.5) |
| Affective distress                          |             |
| Profile of Mood States Total a mean (SD)    | 38 + (8)    |
| Beck Depression Inventory-II mean (SD)      | 9.1 (6.0)   |
| Lifetime psychiatric/substance disorders ++ |             |
| Major depressive disorder +                 | 13 (32.5)   |
| Alcohol +                                   | 15 (37.5)   |
| Cannabis +                                  | 15 (37.5)   |
| Methamphetamine +                           | 17 (42.5)   |
| Cocaine +                                   | 16 (40.0)   |
| Opioid +                                    | 10 (25.0)   |
| Any substance +                             | 25 (62.5)   |

+ Number of cases (%)

++ None met criteria for current abuse/dependence

**Table 2** Baseline medical characteristics ( $n=40$ )

| Characteristic                          | Mean (SD)    |
|---|--------------|
| Hemoglobin                              | 14.2 (1.6)   |
| Platelet count                          | 213.0 (77.2) |
| Albumin                                 | 4.0 (0.4)    |
| Alanine aminotransferase (ALT)          | 85.2 (59.9)  |
| Aspartate aminotransferase (AST)        | 73.2 (48.7)  |
| Bilirubin, total                        | 1.0 (0.2)    |
| AST-to-platelet ratio index (APRI)      | 0.8 (0.5)    |
| HCV RNA (log <sub>10</sub> IU/mL)       | 5.8 (0.7)    |
| HCV genotype                            | n (%)        |
| 1                                       | 28 (70.0)    |
| 2                                       | 6 (15.0)     |
| 3                                       | 5 (12.5)     |
| 4                                       | 1 (2.5)      |
| Fibrosis stage at baseline <sup>a</sup> | n (%)        |
| 0                                       | 10 (28.5)    |
| 1                                       | 12 (34.2)    |
| 2                                       | 2 (5.7)      |
| 3                                       | 5 (14.3)     |
| 4                                       | 6 (17.1)     |

<sup>a</sup> Liver biopsy results available for 35 participants

## Materials and procedure

All participants provided written, informed consent prior to completing a comprehensive neuropsychological, medical, and psychiatric research evaluation at baseline (prior to initiating treatment) and at four follow-up visits. Follow-up visits occurred at approximately 10 weeks, 6 months, 12 months, and 18 months after initiating treatment for HCV. Participants received financial compensation for completing each visit.

## Medical assessment and treatment

All participants were evaluated using structured medical history, physical examination, and laboratory tests at each time point in conjunction with their treatment for HCV. Liver biopsy was conducted for 35 of the 40 (87.5 %) subjects. Treatment regimens followed standard recommendations, i.e., peg-IFN  $\alpha$ -2a (180 mcg via subcutaneous injection/week) as well as daily oral doses of RBV (400–600 mg depending on body weight and HIV status). The mean treatment duration was 36.6 weeks (SD=18.4) and varied by HCV genotype, such that individuals with genotypes 2 and 3 were treated for approximately 24 weeks (mean=27.6, SD=13.4) and individuals with genotype 1 were treated for approximately 48 weeks (mean=40.4, SD=19.1). Individual regimens were altered as indicated by treating physicians. Aspartate aminotransferase (AST) to platelet ratio index (APRI) was calculated as a noninvasive proxy for liver fibrosis at each study visit. Due to the study visit schedule, sustained virologic response (SVR) data (undetectable HCV RNA a full 6 months after completion of therapy) was not available for all participants. Therefore, we instead report the proportion of individuals with undetectable HCV RNA in the serum at their final study visit. Undetectable HCV RNA in serum at the final study visit was achieved by 40.0 % of the sample.

## Neuropsychological assessment

At each visit, participants were administered a comprehensive neuropsychological test battery, which included a measure of estimated premorbid verbal intelligence (i.e., reading portion of the Wide Range Achievement Test—Third Edition [Wilkinson and Robertson 2006]) as well as a relatively brief but robust assessment of the cognitive domains commonly affected by HCV (i.e., learning, memory, verbal fluency, speed of information processing, executive functions, attention/working memory, and motor performance). The neuropsychological battery is detailed in Table 3. Raw scores from individual neuropsychological tests were converted to demographically (e.g., age, education) corrected *T* scores. Wherever possible, neuropsychological test data was also adjusted for ethnicity, utilizing published normative data. These demographically corrected *T* scores were then

**Table 3** Neuropsychological test battery by cognitive domain

|                                 |
|---------------------------------|
| Premorbid verbal intelligence   |
| WRAT-III reading                |
| Attention/working memory        |
| PASAT 50                        |
| WMS-III spatial span            |
| Speed of information processing |
| WAIS-III digit symbol           |
| WAIS-III symbol search          |
| Executive functioning           |
| WCST-64                         |
| TMT Part B                      |
| Learning                        |
| HVLTR Trials 1-3                |
| BVMT-R Trials 1-3               |
| Memory                          |
| HVLTR delayed recall            |
| BVMT-R delayed recall           |
| Motor                           |
| Grooved Pegboard                |
| Verbal fluency                  |
| Letter (FAS)                    |
| Category (animals)              |

*BVMT-R* Brief Visuospatial Memory Test—Revised, *HVLTR* Hopkins Verbal Learning Test—Revised, *PASAT* Paced Auditory Serial Addition Test, *TMT* Trail Making Test, *WAIS-III* Wechsler Adult Intelligence Scale—Third Edition, *WCST-64* Wisconsin Card Sorting Test—64 card version

transformed into deficit scores, which account for both the number and severity of impaired scores in an individual's neuropsychological profile. Domain level deficit scores were then averaged to yield a global deficit score (GDS), or summary index indicating degree of cognitive impairment (Heaton et al. 1994), for each individual at each time point. A cutoff of 0.5 was used to classify individuals as neurocognitively impaired (Carey et al. 2004). In order to assess meaningful global neurocognitive change across several study visits (including corrections for practice effects and regression toward the mean), we used regression-based change scores as continuous variables in our analyses (see Cysique et al. (2009) for a detailed algorithm and validation of this method).

#### Psychiatric and substance use assessment

Participants underwent comprehensive psychiatric assessment at each time point using the Composite International Diagnostic Interview (CIDI version 2.1) (World Health Organization 1998) to generate lifetime diagnoses of mood and substance-related disorders per Diagnostic and Statistical Manual of Mental Disorders (4th ed.) criteria (American

Psychiatric Association 2000). Participants also completed the Beck Depression Inventory-II (BDI-II; Beck 1987) at each study visit. Substance use assessment was augmented at each time point by a separate semistructured follow-back interview.

#### Analytic plan

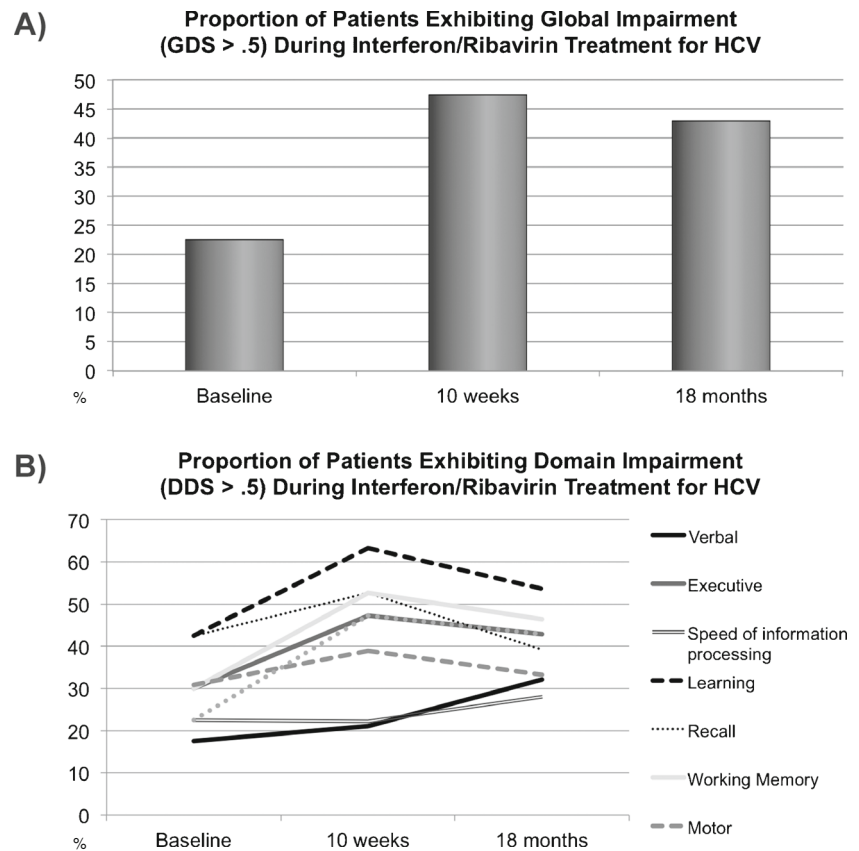
Using the above methodology (Cysique et al. 2009), regression-based change scores were calculated in order to identify reliable changes in neurocognitive functioning over time. From these change scores (indicating severity of declines), global and domain level impairment rates were calculated at each time point in order to estimate the prevalence of clinically meaningful neurocognitive deficits at baseline, 10 weeks, and 18 months after beginning treatment. In order to accommodate departures from normality in individual variable distributions, nonparametric statistical tests were employed, including (1) Wilcoxon signed-rank tests to identify significant changes in cognition, depressive symptoms, and liver fibrosis relative to baseline levels, and (2) Spearman's  $\rho$  to calculate correlations between cognitive performance, depressive symptoms, fatigue, and liver fibrosis at each time point. Finally, clinical and medical variables associated with cognitive decline severity at the univariable level were entered into a least square regression analysis to identify significant independent predictors of neurocognitive worsening. A critical alpha level of 0.05 was set for all analyses.

## Results

### Degree and persistence of neurocognitive change over time

At baseline (prior to IFN/RBV treatment), 22.5 % of the cohort was classified as globally neurocognitively impaired (GDS  $\geq 0.50$ ), which significantly increased to 47.4 % of patients by 10 weeks after initiating treatment ( $p < 0.05$ ; see Fig. 2a). Nearly all of these patients (42.9 %) remained classified as globally impaired after 18 months, and mean GDSs remained significantly elevated relative to baseline levels ( $p < 0.05$ ) at the final study visit. More specifically, these effects were driven by declines within the domains of working memory, learning, and executive functions (see Fig. 2b). Within the domain of attention/working memory, impairment rates increased from 30.0 (baseline) to 52.6 % (10 weeks), reaching 46.4 % at 18 months. Executive impairment rates increased from 30.0 (baseline) to 47.4 % (10 weeks) and 42.9 % at 18 months. Learning impairment rates rose from 42.5 (baseline) to 63.2 % (10 weeks) and 53.6 % at 18 months. Recall impairment rates rose from 42.5 (baseline) to 52.6 % (10 weeks), resolving to 39.3 % at baseline. Motor impairment rates rose from 30.8 (baseline) to 38.9 % (10 weeks), resolving

**Fig. 2** Global and domain level impairments during and after IFN/RBV treatment. **A** Global neurocognitive impairments. After initiating IFN/RBV treatment, the proportion of patients with neurocognitive impairment rose from 22.5 % to 47.4 % at 10 weeks and remained at 42.9% at 18 months after treatment initiation. **B** Domain level neurocognitive impairments. The prevalence and magnitude of incident impairments (during IFN/RBV treatment), and the extent to which these impairments resolved over time, varied substantially by domain. The largest and most persistent declines were observed in the domain of working memory, which remained impaired relative to baseline at 18 months. At 18 months, impaired learning performance was the most prevalent deficit, present in over 50 % of the sample



to 33.3 % at 18 months. Verbal impairment rates were 12.5 % at baseline, 21.1 % at 10 weeks, and 32.1 % after 18 months. With regard to speed of information processing, impairment rates were 22.5 % at baseline and 10 weeks, rising to 28.0 % after 18 months. Figure 3 depicts changes in cognitive performance over time relative to changes in depressive symptoms and liver fibrosis, recorded at each time point. BDI scores at 18-month follow-up did not significantly differ from baseline ( $p > 0.10$ ), and estimated liver fibrosis (APRI) had decreased to significantly below baseline levels by 12 months after treatment initiation (following a mean treatment duration = 36.6 weeks;  $p < 0.05$ ). Cognition (GDS) was not significantly associated with fatigue (POMS subscale) or depressive symptoms (BDI) at any study visit (all  $ps > 0.10$ ). However, baseline BDI score was positively associated with fatigue ratings at 10 weeks and 18 months ( $\rho = 0.54$  and  $0.60$ , respectively).

#### Predictors of neurocognitive decline

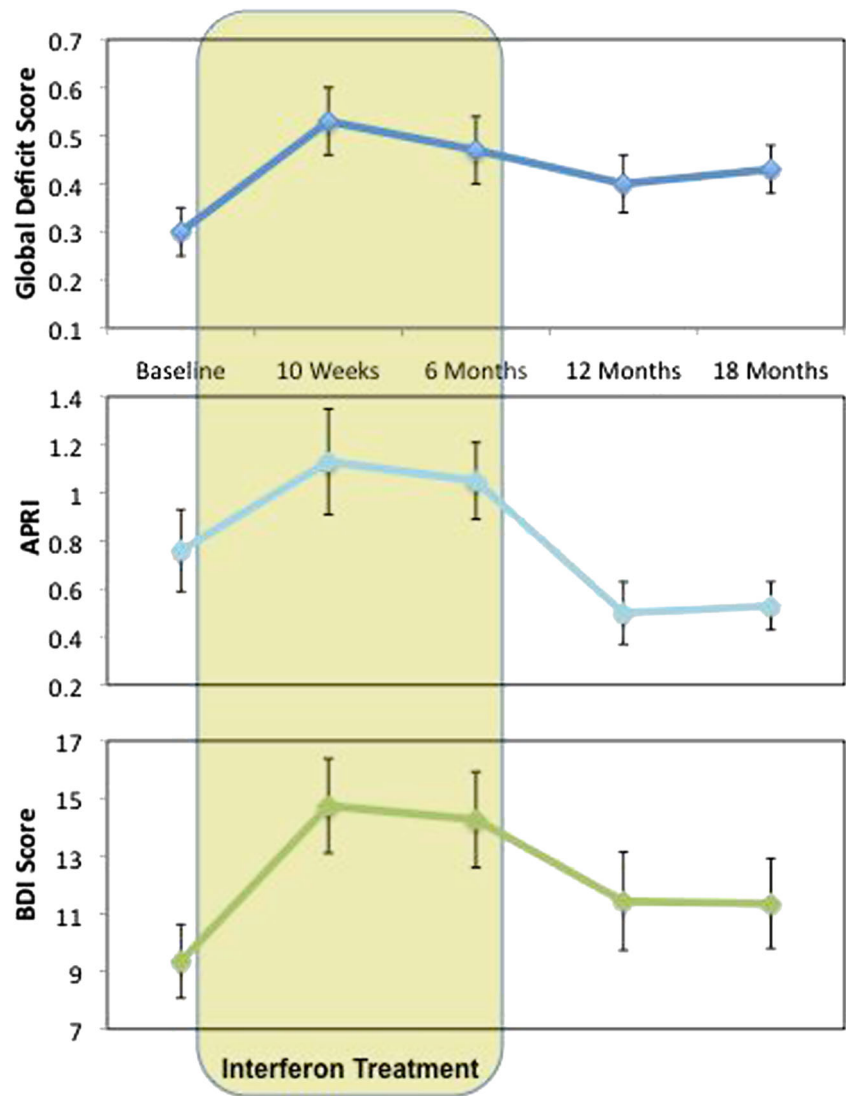
Demographic factors (age, gender, education), current depressive symptoms (BDI), and most medical characteristics (fatigue rating, liver fibrosis, HIV status) were not significantly associated with severity of acute neurocognitive decline (10 weeks) at the univariable level (all  $ps > 0.10$ ). However, infection with HCV genotype 1 and baseline BDI score were significantly associated with acute decline severity ( $ps < 0.05$ ).

After meeting this threshold for inclusion in a least square regression, the resulting model was significant (adjusted  $R^2 = 0.30$ ,  $p = 0.02$ ), indicating that infection with HCV genotype 1 significantly and independently predicted more severe global neurocognitive decline at 10 weeks (standardized  $\beta = -0.42$ ,  $p < 0.05$ ), while baseline BDI-II scores approached significance (standardized  $\beta = 0.36$ ,  $p = 0.08$ ). Higher baseline BDI-II scores were associated with more severe acute declines (Spearman's  $\rho = 0.52$ ,  $p < 0.05$ ). No demographic, medical (treatment duration, undetectable HCV RNA at final study visit, fatigue rating, liver fibrosis, HIV status), or psychiatric characteristics were significantly associated with decline severity after 18 months (all  $ps > 0.10$ ).

#### Conclusions

In this observational study, IFN/RBV-related cognitive declines were prevalent, clinically significant, and most notably, persistent. Nearly half of this naturalistic sample receiving IFN/RBV treatment for HCV exhibited global neurocognitive impairments soon thereafter. While liver function gradually improved and depressive symptoms were alleviated over time, all but one individual exhibiting incident impairment remained globally impaired 6–12 months after completing IFN/RBV treatment. The

**Fig. 3** Cognition, liver fibrosis, and depression before, during, and following IFN/RBV treatment



high frequency of these persistent declines suggests that such impairments may be more commonplace than expected in community samples, in contrast to the widely held belief that neurocognitive symptoms may remit soon after IFN-RBV treatment cessation, or after achieving a favorable virologic response. In this sample, the observed deficits persisted for months after treatment cessation, even in individuals who had achieved virologic suppression (undetectable HCV). Although the observed neurocognitive decrements were modest, the elevated proportion of globally impaired individuals and the persistence of these deficits over time raises the possibility that these declines may be indicative of CNS effects that are slow to reverse, and which may have impacts on quality of life and everyday functioning.

The impact of genotype 1 on cognitive impairments may be imparted via several possible mechanisms, including differences in treatment regimen (e.g., higher cumulative dosage and longer duration). However, these findings are unlikely to be an artifact of dose or duration, which were not significantly associated with genotype or neurocognitive performance,

respectively. We also considered whether hallmark symptoms of IFN treatment (e.g., fatigue, depression) may have been elevated in this group, which may have disproportionately impacted cognitive performance in these individuals. However, this did not appear to be the case, as levels of reported fatigue and depressive symptoms were comparable between genotypes at baseline, on treatment, and after treatment ( $p > 0.10$ ). After ruling out these alternative explanations, we hypothesized that differences in viral genetics or suppression in genotype 1 (potentially related to its frequently chronic course and relative resistance to IFN treatment) may account for the disproportionate association between genotype 1 and neurocognitive impairments observed in our sample. This hypothesis is strengthened by the high prevalence of genotype 1 (88 and 80 %) in several studies that have noted more severe and enduring cognitive effects of IFN treatment for HCV (e.g., 25, 33).

Dose-dependent neurological and neuropsychiatric toxicity has been reported in up to 40 % of patients treated with



combination therapy (Fontana 2000); however, risk factors remain poorly defined (McAndrews et al. 2005). One aim of the current study was to identify predictors of lasting neurocognitive impairment in a sample inclusive of several comorbid risk factors. Our results identified HCV genotype 1 and higher self-reported depressive symptoms at baseline to be predictive of declines at 10 weeks, which is an earlier time point than has been included in most other IFN/RBV studies to date. This may explain why our results (specifically, elevated impairment rates) differ somewhat from investigations that included less acute follow-up time points. Importantly, however, these short-term declines in cognitive functioning do appear to presage longer-term neurocognitive impairment. Our results indicated that cognitive status was not significantly associated with liver disease, a finding that differs from some prior studies (Thein et al. 2007). However, only 11 of 35 (31.4 %) subjects had stage 3 or 4 liver fibrosis, and this may have limited our ability to establish associations. While premorbid depression was identified as a risk factor for more severe early declines, severity of depressive symptoms was not associated with cognitive impairment at any study visit. Thus, having more severe depressive symptomatology at baseline does appear to represent a vulnerability to early and significant adverse treatment effects, whereas depressive symptoms which emerge later in the course of treatment may not necessarily increase risk for persistent cognitive symptoms.

A number of limitations of the current study warrant mention. First, contrary to the results of the current study, other groups have observed improvements or stable performances (Hilsabeck et al. 2005) in certain measures of cognitive function associated with SVR. Further studies with longer post-treatment follow-up are needed to determine whether, when, and to what extent these incident impairments may dissipate. Second, while this study provided comprehensive assessment of cognitive, psychiatric, and medical outcomes over 18 months, it was not a clinical trial (i.e., the study did not control the intervention). Thus, participants ended treatment when medically indicated, rather than at equivalent, predetermined study intervals. In addition, we were not able to include a randomized control (no treatment) group in the study; as such, interpretation of these results should take into account the lack of a directly comparable but untreated group. Third, despite limited exclusion criteria, over half of participants screened for participation were either noncompliant with treatment, ineligible for participation, or lost to follow-up, thereby reducing our sample sizes and restricting our analytic plan. However, it stands to reason that the large number of noncompliant individuals may be related to the very side effects we observed in our sample. Fourth, whereas we were able to evaluate the relationships between cognition, depression, and estimated liver fibrosis over time to a large extent, many subgroup analyses were not adequately powered due to small sample sizes.

Understanding the course of IFN/RBV-related adverse effects has become especially important in recent years, in the context of novel and emerging therapeutics that may hold promise in mitigating neurocognitive and neuropsychiatric sequelae (Forton and Karayiannis 2006). For example, triple combinations involving protease inhibitors (e.g., boceprevir, simeprevir) offer potential improvements in response with shorter treatment latencies, which may potentially reduce cognitive side effects (Zeuzem et al. 2012). While prophylactic antidepressant treatment has been reported to reduce psychiatric symptoms accompanying IFN-based treatments (Kraus et al. 2002; Asnis and De La Garza 2006), the relevance of these data to neurocognitive impairment is not known. Finally, whether novel noninterferon-based therapies (e.g., sofosbuvir/ledipasvir) may improve long-term neurocognitive outcomes will need to be determined (Gane et al. 2012). While these are important directions for future work, it remains to be seen whether decreased treatment durations may mitigate the impacts on cognition that may be sustained by patients with certain risk factors (e.g., HCV genotype 1, premorbid depression). In the meantime, our results suggest that particularly in the context of multiple risk factors, clinicians should monitor cognition throughout the course of treatments for HCV, noting that early declines may identify individuals at elevated risk for persistent neurocognitive impairment.

**Acknowledgments** The Translational Methamphetamine AIDS Research Center (TMARC) is supported by Center award P50DA026306 from the National Institute on Drug Abuse (NIDA) and is affiliated with the University of California, San Diego (UCSD) and the Sanford-Burnham Medical Research Institute (SBMRI). The TMARC comprised the following: Director—Igor Grant, M.D.; Co-Directors—Ronald J. Ellis, M.D., Ph.D., Cristian L. Achim, M.D., Ph.D., and Scott L. Letendre, M.D.; Center Manager—Steven Paul Woods, Psy.D.; Assistant Center Manager—Aaron M. Carr, B.A.; Clinical Assessment and Laboratory (CAL) Core: Scott L. Letendre, M.D. (Core Director), Ronald J. Ellis, M.D., Ph.D., Rachel Schrier, Ph.D.; Neuropsychiatric (NP) Core: Robert K. Heaton, Ph.D. (Core Director), J. Hampton Atkinson, M.D., Mariana Cherner, Ph.D., Thomas D. Marcotte, Ph.D., Erin E. Morgan, Ph.D.; Neuroimaging (NI) Core: Gregory Brown, Ph.D. (Core Director), Terry Jernigan, Ph.D., Anders Dale, Ph.D., Thomas Liu, Ph.D., Miriam Scadeng, Ph.D., Christine Fennema-Notestine, Ph.D., Sarah L. Archibald, M.A.; Neurosciences and Animal Models (NAM) Core: Cristian L. Achim, M.D., Ph.D. (Core Director), Eliezer Masliah, M.D., Stuart Lipton, M.D., Ph.D.; Administrative Coordinating Core (ACC)—Data Management and Information Systems (DMIS) Unit: Anthony C. Gamst, Ph.D. (Unit Leader), Clint Cushman (Unit Manager); ACC—Statistics Unit: Ian Abramson, Ph.D. (Unit Leader), Florin Vaida, Ph.D., Reena Deutsch, Ph.D., Anya Umlauf, M.S.; ACC—Participant Unit: J. Hampton Atkinson, M.D. (Unit Leader), Jennifer Marquie-Beck, M.P.H. (Unit Manager); Project 1: Arpi Minassian, Ph.D. (Project Director), William Perry, Ph.D., Mark Geyer, Ph.D., Brook Henry, Ph.D.; Project 2: Amanda B. Grethe, Ph.D. (Project Director), Martin Paulus, M.D., Ronald J. Ellis, M.D., Ph.D.; Project 3: Sheldon Morris, M.D., M.P.H. (Project Director), David M. Smith, M.D., M.A.S., Igor Grant, M.D.; Project 4: Svetlana Semenova, Ph.D. (Project Director), Athina Markou, Ph.D., James Kesby, Ph.D.; Project 5: Marcus Kaul, Ph.D. (Project Director). The views expressed in this article are those of the authors

and do not reflect the official policy or position of the United States Government. We have no commercial affiliations or consultancies which might be construed as conflicts of interest. Financial support: NIH (P50-DA026306), P01 DA12065, P30-MH062512.

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