Published in final edited form as:
J Int Neuropsychol Soc. 2009 January ; 15(1): 69–82. doi:10.1017/S1355617708090085.

The cognitive effects of hepatitis C in the presence and absence of a history of substance use disorder

Marilyn Huckans[1,2,3], **Adriana Seelye**[1,4], **Tiffany Parcel**[1,4], **Lisa Mull**[1,4], **Jonathan Woodhouse**[1,5], **Danell Bjornson**[1,6], **Bret E. Fuller**[1,2], **Jennifer M. Loftis**[1,2,3,7], **Benjamin J. Morasco**[2,3], **Anna W. Sasaki**[1,8], **Daniel Storzbach**[2], and **Peter Hauser**[1,2,3,7,8,9]

[1]Northwest Hepatitis C Resource Center, Portland VA Medical Center, Portland, Oregon

[2]Behavioral Health & Clinical Neurosciences Division, Portland VA Medical Center, Portland, Oregon

[3]Department of Psychiatry, Oregon Health and Science University, Portland, Oregon

[4]Department of Psychology, Pacific University, Portland, Oregon

[5]Department of Psychology, George Fox University, Portland, Oregon

[6]School of Nursing, Oregon Health and Science University, Portland, Oregon

[7]The JENS Lab, Portland VA Medical Center, Portland, Oregon

[8]Department of Internal Medicine, Oregon Health and Science University, Portland, Oregon

[9]Department of Behavioral Neurosciences, Oregon Health and Science University, Portland, Oregon

Abstract

The aim of the study was to determine whether infection with the hepatitis C virus (HCV) is associated with cognitive impairment beyond the effects of prevalent comorbidities and a history of substance use disorder (SUD). Adult veterans were recruited from the Portland Veterans Affairs Medical Center into three groups: (1) HCV+/SUD+ (n = 39), (2) HCV+/SUD− (n = 24), and (3) HCV−/SUD− (n = 56). SUD+ participants were in remission for ≥90 days, while SUD− participants had no history of SUD. Groups did not significantly differ in terms of rates of psychiatric or medical comorbidities. Procedures included clinical interviews, medical record reviews, and neuropsychological testing. Significant group differences were found in the domains of Verbal Memory, Auditory Attention, Speeded Visual Information Processing, and Reasoning/Mental Flexibility ($p \leq .05$). *Post hoc* comparisons indicated that HCV+/SUD− patients performed significantly worse than HCV−/SUD− controls on tests measuring verbal learning, auditory attention, and reasoning/mental flexibility, but only HCV+/SUD+ patients did worse than HCV−/SUD− controls on tests of speeded visual information processing. Results indicate that chronic HCV is associated with cognitive impairment in the absence of a history of SUD. The most robust deficits appear to be in verbal learning and reasoning/mental flexibility. (*JINS*, 2009, *15*, 69–82.)

Correspondence and reprint requests to: Marilyn Huckans, Portland VA Medical Center (P3MHDC), 3710 SW US Veteran's Hospital Road, Portland, OR 97239. marilyn.huckans@va.gov.

Keywords

Neuropsychology; Delirium; Dementia; Amnestic; Cognitive disorders; Infectious hepatitis virus; Substance-related disorders; Depression; Pain

INTRODUCTION

Chronic hepatitis C virus (HCV) infects approximately 2.2% of adults worldwide ("Global burden of disease (GBD) for hepatitis C", 2004) and 5.4% of U.S. veterans seeking health care through facilities in the Veterans Healthcare Administration (Dominitz et al., 2004). The majority of individuals with HCV remain asymptomatic or report a range of mild-to moderate symptoms including flu-like symptoms, cognitive difficulty, and psychiatric disorder (Seeff & Hoofnagle, 2003). More serious medical complications can occur, however, and an estimated 10–15% of patients with HCV progress to advanced liver disease, including cirrhosis and hepatocellular carcinoma (Seeff & Hoofnagle, 2003).

Virological Theories of HCV-Associated Cognitive Impairment

HCV+ patients frequently *report* cognitive complaints, and several mechanisms leading to HCV-associated cognitive impairment have been previously proposed (Collie, 2005; Forton et al., 2003, 2006; Laskus et al., 2005). *Virological theories* posit that HCV disease processes alter central nervous system (CNS) function and impair cognition. For example, a "trojan horse" model suggests that HCV infects peripherally circulating monocyte-derived macrophages, which can travel across the blood–brain barrier (BBB). Although not yet conclusive, in support of this theory, several studies have found evidence for HCV replication in the brain (Forton et al., 2004; Laskus et al., 2002; Maggi et al., 1999; Morsica et al., 1997; Radkowski et al., 2002).

Alternatively, although peripheral cytokines are unlikely to passively diffuse through the BBB, HCV-induced peripheral immune activation could trigger central cytokine dysregulation *via* several mechanisms independent of the presence of HCV within the brain (Maier, 2003; Wilson et al., 2002): cytokines may enter through areas of the brain with weak BBB (e.g., circumventricular regions or choroid plexuses); peripheral cytokines may activate central cytokine production by binding to Receptors in the cerebral vasculature; or, through active transport of cytokines across the BBB. In support of virological theories of HCV-associated cognitive impairment, several studies have found cerebral metabolite abnormalities in HCV+ patients using *in vivo* magnetic resonance spectroscopy (MRS) (Forton et al., 2001; McAndrews et al., 2005; Taylor et al., 2004; Weissenborn et al., 2004), as well as downregulation of mitochondrial oxidative phosphorylation genes and some ribosomal protein genes in brain tissue of HCV+ patients (Adair et al., 2005).

Although more specific mechanisms have yet to be confirmed, virological theories of HCV-associated cognitive impairment generally share a hypothesis that central immune activation in part mediates the relationship between chronic HCV infection and cognitive impairment. Because subjective cognitive complaints do not always correlate with objective performance on cognitive tests (Hilsabeck et al., 2003), a critical first step toward validating a virological model is confirmation that HCV+ patients have measurable neuropsychological deficits upon testing.

To our knowledge, eight published studies have previously used neuropsychological tests to compare HCV+ adults with HCV– controls without advanced liver disease (Cherner et al., 2005; Cordoba et al., 2003; Forton et al., 2002; Karaivazoglou et al., 2007; Letendre et al., 2005; Martin et al., 2004; McAndrews et al., 2005; von Giesen et al., 2004; Weissenborn et

al., 2004); see Table A1 for a summary of sample characteristics and findings. These studies vary markedly in their inclusion criteria, type of control group, statistical design, and choice and breadth of neuropsychological tests. Methodological differences, therefore, likely contribute to inconsistent findings across studies, particularly in the type and extent of cognitive impairments found. Of these eight studies, seven found that HCV+ patients with mild liver disease performed worse than HCV− controls in at least one cognitive domain. Thus, the preponderance of the evidence suggests that infection with chronic HCV is associated with increased risk for a range of cognitive impairments. Establishing a clear profile of HCV-associated cognitive impairment, however, still requires replication and integration of previous findings.

Nonvirological Theories of HCV-Associated Cognitive Impairment: Addressing Substance Use Disorders and Psychiatric and Medical Comorbidities

In contrast to the seven positive studies cited in Table A1, the remaining negative study found that HCV+ patients performed no differently than HCV− controls; only HCV+ patients with decompensated cirrhosis evidenced worse performance (Cordoba et al., 2003). Although reasons for this incongruent finding remain unclear, its sample contrasted with other studies in terms of its low proportion of subjects with a history of intravenous drug use (IVDU) and its careful exclusion of patients with currently symptomatic medical comorbidities. This, of course, raises the possibility that HCV-associated cognitive impairment may be related to medical or substance use history rather than HCV itself. Indeed, an earlier study compared 66 HCV+ patients to 14 HCV− controls with other types of liver disease on measures of cognitive functioning (Hilsabeck et al., 2002). Only the subgroup of HCV+ patients with medical comorbidities exhibited cognitive impairment, while the HCV+ patients with no medical comorbidities did not differ from HCV− controls. While this study suggests that, for patients without medical comorbidities, the severity of HCV-associated cognitive impairment may not exceed the impairment level known to be associated with other types of liver disease (Collie, 2005), it remains unclear how the HCV+ patients may have compared to HCV− controls without liver disease.

Despite limitations, these latter two studies highlight the importance of testing *nonvirological theories* of HCV-associated cognitive impairment, which propose that cognitive difficulties are caused secondarily by other symptoms of HCV or other comorbidities. For example, HCV+ patients have high rates of substance use disorders (SUDs), psychiatric disorders, and medical conditions, each of which can be risk factors for cognitive impairment in normal populations (Huckans et al., 2005, 2006; Loftis et al., 2006). Advanced liver disease and hepatic encephalopathy have also been associated with cognitive impairment in both HCV− and HCV+ populations (Collie, 2005; Forton et al., 2006). Additionally, although few studies have examined the cognitive effects of interferon-alpha therapy for HCV, aspects of neuropsychological functioning may decline during antiviral treatment (Hilsabeck et al., 2005; Kraus et al,. 2005; Lieb et al., 2006). These variables may serve as confounding factors, which could lead to spurious associations between HCV status and cognitive impairment.

Previous studies have inconsistently controlled for aspects of current or recent substance abuse, advanced liver disease, and current or past interferon therapy. However, no published studies have comprehensively ruled out *history* of alcohol or drug use disorders as a confounding factor, likely in large part due to the difficulty of finding a sample of HCV+ patients with no history of SUD. Indeed, the most common transmission route for HCV is IVDU, accounting for approximately 65–70% of patients with HCV (Seeff & Hoofnagle, 2003). In one sample of 11,854 veterans who tested positive for HCV, medical record databases indicated that 64% had a history of SUD, the most common diagnoses including alcohol (58%), polysubstance (44%), cocaine (18%), and opioid (16%) abuse (Huckans et

al., 2005). This indicates that HCV+ populations largely comprise previously addicted adults.

Previous studies examining the relationship between cognitive functioning and HCV status have only partially addressed current or past alcohol or drug abuse, likely because each study was designed with other purposes and strengths in mind. However, given the vast literature on the potentially long-term cognitive effects of SUDs (Moselhy et al., 2001; Verdejo-Garcia et al., 2004; Vik et al., 2004), the question remains whether HCV-associated cognitive impairment is a spurious association with history of SUD. The *primary objective* of this study, therefore, was to determine whether HCV+ patients exhibit cognitive impairment in the absence of any history of alcohol or drug use disorder. To our knowledge, our study is the first to specifically include groups of HCV+ patients with and without a history of SUD for this purpose. A *secondary objective* was to examine cognitive deficits associated with HCV status above and beyond impairments caused by other psychiatric and medical comorbidities.

METHOD

Research Participants

A total of 119 patients were recruited from the Portland Veterans Affairs Medical Center (PVAMC) into three study groups: (1) patients with current HCV and no history of SUD (HCV+/SUD−, $n = 24$), (2) patients with current HCV as well as a history of SUD, currently in remission for at least 90 days (HCV+/SUD+, $n = 39$), and (3) patients with no history of HCV or SUD (HCV−/SUD−, $n = 56$). Patients were deemed to have a history of SUD if they ever met Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Tex Revision (DSM-IV-TR) (American Psychiatric Association, 2000) criteria for alcohol or drug abuse or dependence. All patients in the HCV+ groups had evidence in their medical record of a detectable HCV load based on polymerase chain reaction tests.

Participants were excluded for the following criteria: (1) History of a major medical condition, or currently unstable medical condition, that is likely to be associated with severe neurological or immune dysfunction currently [e.g., stroke, seizures, brain tumors, Parkinson's disease, neurodegenerative dementia, mental retardation, hepatic encephalopathy, human immunodeficiency virus (HIV)]. In the interest of generalizability to typical HCV+ populations, participants with well-controlled or stable conditions were included as long as severe cognitive effects were not currently suspected (e.g., well-controlled diabetes, hypertension, or asthma). (2) History of traumatic brain injury with known loss of consciousness ≥30 min. (3) Use of alcohol, illicit substances, or medications with acute cognitive effects such as sedation or intoxication (e.g., benzodiazepines, opiates, muscle relaxants) on the day of testing. (4) Advanced liver disease as indicated by any of the following: (a) classified as having stage 4 liver disease or grade 4 inflammation upon biopsy, (b) classified by a hepatologist as having probable decompensated cirrhosis based on clinical indicators and standard liver labs, or (c) Aspartate aminotransferase (AST)-to-platelet ratio index (APRI) ≥1.5. The APRI has been previously validated for use in HCV research, and values ≥1.5 reliably predict both liver fibrosis and cirrhosis (Lackner et al., 2005; Wai et al., 2003). (5) Current pregnancy. (6) History of schizophrenia or schizoaffective disorder, current psychotic or manic episode, or currently unstable and severe psychiatric disorder. In the interest of generalizability to typical HCV+ populations, patients with other current psychiatric diagnoses were included as long as present symptoms did not preclude valid cognitive testing. (7) History of interferon therapy or chemotherapy.

Potential subjects were informed of the study *via* study advertisements posted throughout the hospital, mailed to patients who participated in previous HCV research, or distributed by

providers. Interested patients contacted study coordinators by phone and were screened for eligibility. No data were maintained on patients prior to consent. Following consent, two subjects in the HCV+/SUD+ group were excluded for probable decompensated cirrhosis based on standard liver labs, and nine other subjects were excluded based on an APRI ≥1.5 (seven HCV+/SUD+, one HCV+/SUD−, and one HCV−/SUD−), yielding our final sample of 119 subjects.

Procedures

All research was conducted with permission from PVAMC's institutional review board and in accordance with the Helsinki Declaration. All patients were paid $30 to complete the following study procedures: clinical interview, comprehensive medical record review, psychological questionnaires, and a comprehensive neuropsychological testing battery. All study procedures were administered by one of four advanced doctoral candidates in clinical psychology; all graduate students (AS, TP, LM, JW) were trained and supervised by a clinical neuropsychologist (MH).

Clinical interviews were conducted using a structured case report form, developed specifically for this study, including prompts to screen patients based on each inclusion criteria, gather relevant demographic data, assess for a full range of current and past Axis I psychiatric disorder and SUD using DSM-IV-TR (American Psychiatric Association, 2000) criteria, evaluate for history of head injuries, and record a comprehensive list of current and previous medical conditions. Study personnel additionally reviewed each participant's complete electronic medical record to collect recent medical laboratory results and to cross-validate data gathered in the clinical interview.

Patients also completed several psychological questionnaires. The Beck Depression Inventory assessed current depression (Beck et al., 1996). The Severity of Dependence Scale (SDS) measured substance abuse severity (Gossop et al., 1995). Patients were also asked to rate their current pain on a 10-point Likert scale from minimal (1) to severe (10).

The neuropsychological battery included well-validated and widely available measures testing a full range of cognitive domains. Raw scores were converted to standard scores based on norms that corrected for age, gender, race, and years of education, as appropriate. Table A2 lists subtests by cognitive domain along with the respective normative samples and type of standard score referenced.

Standard neuropsychological scores were then converted to global and domain-specific deficit scores using methods adapted from those previously described for use with HIV+ and HCV+ populations (Carey et al., 2004; Cherner et al., 2005; Heaton et al., 1995; Letendre et al., 2005). In brief, standard subtest scores were assigned a deficit rating as follows: $z \geq -0.5 = 0$ points, $-1.0 \leq z < -0.5 = 1$ point, $-1.5 \leq z < -1.0 = 2$ points, $-2.0 \leq z < -1.5 = 3$ points, or $z < -2.0 = 4$ points. Domain-specific deficit scores were then calculated by summing composite deficit ratings and dividing by the total number of tests within a domain; the global deficit score was calculated as the average deficit rating across tests in the battery. Domain-specific and global deficit scores ≥0.5 were classified as impaired. A deficit score serves as an objective summary of both the number and severity of impaired performances within a domain or battery. Although less weight is given to normal performances, this approach provides a more reliable and conservative measure for between-group comparisons than individual standard scores because each deficit score is based on multiple tests within a domain or battery, enhancing convergent validity and reducing experiment-wise error.

To ensure accuracy, all psychological and neuropsychological tests were scored and entered into databases twice by separate study personnel.

Data Analysis

All analyses were conducted with SPSS (version 15). *p* Values ≤.05 were considered significant.

Primary analyses—Between-group analyses of demographic variables were conducted using analysis of variance (ANOVA) and *post hoc* Scheffe tests for continuous variables; for binary responses, we used three-sample Kruskal–Wallis tests because multiple cells contained low frequencies (<5). Between-group analyses of neuropsychological performance were conducted using multivariate analysis of variance (MANOVA) and *post hoc* Scheffe tests. For each cognitive domain, all relevant standardized subtest scores were entered as multiple dependent variables, and study group was entered as the independent variable. A multivariate effect (Wilks' Lamda) for each cognitive domain was reported as well as the univariate *F* and *p* values for each subtest. An ANOVA, however, was used for the Visuoconstruction domain because it contained only one subtest. Finally, we used Kruskal–Wallis tests to compare groups in terms of rates of impairment based on domain-specific deficit scores.

***Post hoc* exploratory analyses—**Pearson *R* correlations were used to explore the relationship between several additional variables of interest (estimated cognitive reserve, depression, and pain) and performance on neuropsychological tests. For cognitive domains found to have significant multivariate effects in the primary analyses, these three variables of interest were also entered as covariates in a series of multivariate analyses of covariance (MANCOVAs) with study group entered as the independent variable and relevant subtests entered as the multiple dependent variables.

RESULTS

Demographic and Clinical Characteristics

Table 1 summarizes demographic data for the total sample and by group. Groups did not significantly differ in terms of age or race. Although the SUD+ group included a significantly higher percentage of men than the SUD− groups, all groups were composed primarily of men (89.1% male in total sample). The HCV+ groups had completed significantly fewer years of education than the HCV− group. Groups did not significantly differ in rates of current psychiatric diagnoses or medical conditions.

The HCV+/SUD+ group (*n* = 39) included patients with at least 90 days of remission, but most patients reported several years of sobriety (average years since remission = 8.4 ± 7.6). Prior to remission, most patients reported many years of abuse (average years of abuse = 18.2 ± 11.9), at an average level of abuse which could be categorized as moderate (average SDS score = 7/25 ± 3). Patients met criteria for previous abuse of or dependence on the following substances: alcohol (87.2%), stimulants (79.5%), marijuana (55.3%), opiates (51.3%), hallucinogens (7.7%), and other drugs of abuse (7.7%). Because most patients reported polysubstance abuse (89.7%), these categories are not mutually exclusive.

Within the HCV+/SUD− group (*n* = 24), the following risk factors were reported as the most likely HCV transmission route: blood transfusion (20.8%, *n* = 5), accidental exposure at work (20.8%, *n* = 5), blood exposure during combat (8.3%, *n* = 2), and other or unknown risk factors (37.5%; two plasma or blood donations, one military immunization, one tattoo, and five unknown). Although three (12.5%) remaining individuals in the HCV+/SUD− group reported contracting HCV *via* remote IVDU, their reported use was described as infrequent and experimental only, and none of these individuals ever met criteria for SUD of any type. Within the HCV+/SUD+ group (*n* = 39), the following risk factors were reported

as the most likely transmission route: IVDU (64.1%, *n* = 25), accidental exposure at work (10.3%, *n* = 4), blood transfusion (7.7%, *n* = 3), blood exposure during combat (7.7%, *n* = 3), and other or unknown risk factors (10.3%; one military immunization and three unknown).

There were no statistical differences between the HCV+/ SUD− or HCV+/SUD+ groups in terms of viral load [HCV RNA($\log_{10}$ IU/ml) = 6.2 ± 0.6, HCV+/SUD− *vs*. 6.3 ± 0.9, HCV+/ SUD+], serum aspartate aminotransferase levels (AST = 47.9 ± 26.3, HCV+/SUD− *vs*. 45.9 ± 27.5, HCV+/ SUD+), platelet levels (PLT = 238.5 ± 68.6, HCV+/SUD− *vs*. 235.6 ± 66.4, HCV+/SUD+), or APRI values (APRI = 0.48 ± 0.3, HCV+/SUD− *vs*. 0.48 ± 0.3, HCV+/ SUD+). Within the HCV+/SUD− group, 14/24 subjects had HCV genotypes available in their records (thirteen with genotype 1 and one with genotype 2). Within the HCV+/SUD+ group, 18/39 had available genotypes (nine with genotype 1, six with genotype 2, two with genotype 3, and one with genotype 4). Only 3/24 subjects in the HCV+/SUD− group and 8/39 subjects in the HCV+/SUD+ group had liver biopsy results available in their record; none of these subjects were assessed above stage 2 in terms of fibrosis or grade 2 in terms of cirrhosis.

Primary Analyses: Comparisons of Neuropsychological Performance by Cognitive Domain

As summarized in Table 2, significant group differences were found in terms of standardized scores in the Verbal Memory, Auditory Attention, Speeded Visual Information Processing, and Reasoning/Mental Flexibility domains (all *p* values ≤.05). *Post hoc* comparisons indicated that the HCV+/ SUD− group performed significantly worse than HCV−/SUD− controls on subtests measuring verbal learning [California Verbal Learning Test (CVLT)-II Total Immediate Recall], auditory attention [Wechsler Adult Intelligence Scale—third edition (WAIS-III) Digit Span and Letter Number Sequencing], and reasoning/ mental flexibility [Delis– Kaplan Executive Functioning Scale (D-KEFS) Sorting and WAIS-III Matrix Reasoning] but not on subtests in the Speeded Visual Information Processing domain. The HCV+/ SUD+ group performed significantly worse than HCV−/ SUD− controls on subtests measuring verbal learning (CVLT-II Total Immediate Recall), speeded visual information processing (WAIS-III Digit Symbol), and reasoning/mental flexibility (D-KEFS Sorting, D-KEFS Proverbs, and WAIS-III Matrix Reasoning). No other *post hoc* comparisons yielded significant between-group differences. Thus, the HCV+/ SUD − and HCV+/SUD+ groups did not significantly differ in terms of performance on any neuropsychological subtests. MANOVAs revealed no significant group differences in terms of standardized scores in the Language, Visuospatial Memory, Motor Speed, or Visuomotor Construction domains (*p* values >.05).

As summarized in Table 3 and Table 4, groups significantly differed in terms of rates of impairment in the Verbal Memory and Reasoning/Mental Flexibility domains; both HCV+ groups had higher rates of impairment on these domains than did the HCV− controls.

Post Hoc Exploratory Analyses: Between-Group Comparisons on Other Variables of Interest

As summarized in Table 5, compared with HCV− controls, the HCV+ groups scored significantly lower on Wide Range Achievement Test, third edition (WRAT3) Reading (Wilkinson (1993). The HCV+ groups also reported significantly higher levels of current pain, and the HCV+/SUD+ group reported significantly more depressive symptoms than HCV− controls. Lower WRAT3 Reading scores, fewer years of education, more depressive symptoms, and higher pain ratings each significantly correlated with poorer performance on a variety of neuropsychological tests. Pearson product moment correlations ranged from −.

130 to .428 for WRAT3 Reading, from −.195 to .340 for years of education, from −.363 to .054 for depression, and from −.338 to .079 for pain.

For each cognitive domain, Table 6 lists the *p* values from a series of MANCOVAs with cognitive reserve, depression, or pain entered as separate covariates and HCV status entered as the independent variable. For each subtest, Table 6 also lists the *p* values from the univariate *F* tests. Cognitive reserve was estimated using both WRAT3 Reading and years of education for the purposes of these *post hoc* covariate analyses. The superscripts in Table 6 indicate the significant covariates for each test (covariates with *p* values of <.05 are indicated by D = depression, W = WRAT3, E = education, and P = pain.) Consistent with primary analyses, when either depression or pain was entered as a covariate, significant multivariate effects of HCV status on cognition were found for Verbal Memory, Auditory Attention, Speeded Visual Information Processing, and Reasoning/Mental Flexibility. When cognitive reserve was entered as a covariate, multivariate effects for Verbal Memory and Speeded Visual Information Processing remained significant; however, the multivariate effects for Auditory Attention and Reasoning/Mental Flexibility were no longer significant. As summarized in Table 6, all three covariates (pain, depression, and cognitive reserve) were found to have significant effects on a range of cognitive domains and tests.

DISCUSSION

The primary objective of the present study was to determine whether chronic infection with HCV is associated with cognitive impairment, particularly in the absence of any history of SUD. To this end, our study specifically recruited a group of HCV+ patients with no history of SUD. Because IVDU is the primary transmission route for HCV, and because the majority of HCV+ patients in the United States have a history of SUD (Huckans et al., 2005; Seeff & Hoofnagle, 2003), our findings are a relevant extension of previous work on HCV-associated cognitive impairment. In selecting patients, we minimized major cognitive risk factors by excluding patients with decompensated cirrhosis; active substance abuse within the past 3 months; and severe or unstable medical and psychiatric disorders such as stroke, traumatic brain injury, and psychosis. However, in order to maximize generalizability to typical HCV+ populations, we included patients with common and reasonably controlled psychiatric and medical diagnoses. Thus, we expanded upon prior research by using a control group with no history of SUD and by carefully controlling for other factors that may be associated with cognitive impairment.

Overall, our results are generally consistent with previous studies that have identified cognitive impairment among HCV+ patients. Specifically, we found that HCV+/SUD− participants performed significantly worse than HCV−/SUD− controls on tests of verbal learning, auditory attention, and reasoning/mental flexibility, indicating that these HCV-associated cognitive impairments are not attributable to history of substance abuse. HCV+/SUD+ participants also performed significantly worse than HCV−/SUD− controls on tests of speeded visual information processing. Since the HCV+/SUD− group performed similarly to the HCV−/SUD− controls on speeded visual information processing tests, lower performance by the HCV+/SUD+ group in this domain may be attributable to history of SUD rather than HCV status.

When comparing our domain-specific cognitive results to results from other positive studies (Table A1), important consistencies as well as variations emerge. All studies that included measures of verbal learning/memory and reasoning/mental flexibility, including our own study, found HCV-associated impairments in these domains, indicating that these impairments are rather robust among HCV+ patients. Neither our study nor any previous study found HCV-associated impairments in language/fluency or visuomotor construction,

indicating that HCV is unlikely to produce deficits in these areas. Results in Visuospatial Memory, Auditory Attention, Speeded Visual Information Processing, and Motor Speed domains, however, vary considerably across studies. Although we are unable to definitively confirm reasons for these interstudy domain-specific variations with our current study design, one hypothesis is that these impairments tend to be less robust among HCV+ patients and that the relatively small sample sizes, typically ~20–40 per group, among previously published studies have not provided for adequate power to reliably detect group differences in these domains. Alternatively, because studies vary markedly in terms of sampling characteristics, positive findings in these domains could represent effects of other medical and psychiatric comorbidities or interactions between these comorbidities and HCV.

Regardless, our own results, combined with findings from previous studies, suggest that the most robust impairments among patients with HCV appear to be in the areas of verbal learning and reasoning/mental flexibility. Indeed, we found that within our own sample, 41.7% of HCV+/SUD− patients and 33.3% of HCV+/SUD+ patients evidenced impairments in verbal learning, compared with 16.1% of HCV− patients. Likewise, 25.0% of HCV+/SUD− patients and 20.5% of HCV+/SUD+ patients evidenced impairments in reasoning/mental flexibility, as compared with 5.4% of HCV− patients.

Although we found some evidence for HCV-associated impairments in speeded visual information processing and auditory attention, these findings should be interpreted cautiously for several reasons. First, previous studies (Table A1) have not consistently found impairments in these domains. Second, the HCV+/SUD− group performed similarly to the HCV−/SUD− group on tests of speeded visual information processing. Last, the HCV+ groups did not significantly differ from our HCV− controls in terms of rates of impairments on the Speeded Visual Information Processing or Auditory Attention domain. Thus, future studies are needed to replicate and clarify outcomes in these domains.

One limitation of our current study design is that it is does not allow for direct confirmation of virological mechanisms that could lead to HCV-associated cognitive impairment. For example, although we excluded patients with probable advanced liver disease based on biopsy, liver labs, and APRI scores, we could not definitively rule out hepatic encephalopathy as a contributing cognitive risk factor in our HCV+ groups because, due to prohibitive costs, not all patients underwent liver biopsies and no measure of portal vein hypertension was included. Nevertheless, our results indicate that HCV-associated cognitive impairments, particularly in the areas of verbal learning and reasoning/mental flexibility, are not likely attributable to nonvirological causes such as common medical and psychiatric comorbidities or history of substance abuse. Our cognitive findings appear to be consistent with previous MRS studies that found metabolic abnormalities in frontostriatal regions including the basal ganglia (Forton et al., 2001, 2002) and central white matter (McAndrews et al., 2005). However, additional imaging studies, such as those using functional magnetic resonance imaging or diffusion tensor imaging (DTI) techniques, are needed to better delineate the anatomical correlates of HCV-associated cognitive impairments. Future studies are also needed to identify mechanisms, particularly the possibility of central inflammatory processes, that could lead to HCV-associated anatomical and functional changes within the CNS.

Another limitation of the present study is that its design precludes meaningful exploration of SUD effects on neuropsychological functioning in an HCV+ population. Indeed, it is not surprising that we found no differences between our HCV+/SUD− and HCV+/SUD+ groups in terms of neuropsychological performance on any test because within the HCV+/SUD+ group, (1) SUD history was rather remote, (2) substances were mixed, and (3) abuse and dependence were combined. These characteristics enabled us to more clearly demonstrate

HCV-associated cognitive effects in the absence of an SUD. However, these same characteristics likely explain why we did not find an additive SUD effect in our sample.

One issue that arises when studying HCV-associated cognitive impairment is how to address severity of other current HCV-associated symptoms such as depression, fatigue, and pain. These variables have each been identified as risk factors for cognitive impairment in HCV− populations, but relationships between these factors and cognition may be bidirectional, and etiologies are likely multifactorial and complex (Martelli et al., 2004; Michiels & Cluydts, 2001; Pfennig et al., 2007; Porter et al., 2007; Weissenborn et al., 2004). Moreover, returning to a virological model of HCV-associated cognitive impairment, it may be hypothesized that chronic immune activation in HCV+ patients causes a constellation of symptoms including depression, fatigue, pain, and cognitive dysfunction; intercorrelations between these variables would be expected if they do indeed represent symptoms of the same syndrome. Thus, controlling for these other symptoms could remove common variance resulting from HCV-induced immune activation, masking true significant effects on cognition and producing a type II error.

Despite this dilemma, neuropsychological outcomes before and after controlling for other relevant HCV-associated symptoms remain clinically relevant and theoretically interesting. Typical HCV+ populations have high rates of these other symptoms, and knowledge of the relative risk of cognitive impairment based on other symptoms may be beneficial. Although three studies cited in Table A1 found no significant differences among groups in terms of current depression ratings (Cherner et al., 2005;Cordoba et al., 2003;Karaivazoglou et al., 2007), three other studies found higher levels of depression among HCV+ patients compared with HCV− controls (Forton et al., 2002;McAndrews et al., 2005;Weissenborn et al., 2004). None of these studies statistically controlled for severity of depression when analyzing the relationship between HCV status and cognition. Moreover, although recent findings suggest that HCV+ patients report high rates of pain disorders (Silberbogen et al., 2007; Whitehead et al., in press), no published studies have specifically examined the relationship between pain and cognition in HCV+ patients.

While it is beyond the scope of the present study to verify the direction of the relationships between HCV status, cognitive functioning, and severity of other current HCV-associated symptoms, we used *post hoc* exploratory analyses to examine the extent to which HCV status is associated with cognitive impairment before and after controlling for severity of current depressive symptoms or pain. We found that multivariate and univariate effects of HCV status on cognition remained significant for several tests of verbal learning, auditory attention, speeded visual information processing, and reasoning/mental flexibility, even when pain or depression was entered as a covariate. These results were consistent with our primary analyses and with the conclusions of previous studies (Table A1), suggesting that HCV-associated cognitive impairment exists above and beyond the effects of either current depressive symptoms or pain.

An additional problem that arises when examining neuropsychological functioning within any medical population is how to measure and whether to control for estimates of cognitive reserve. An expanding body of literature reveals that within a variety of medical populations at risk for cognitive impairment (e.g., Alzheimer's disease, HIV, lead exposure, post-coronary artery bypass surgery), individuals with low cognitive reserve evidence significantly higher rates of cognitive impairment and faster decline than individuals with high cognitive reserve (Bleecker et al., 2007; Pereda et al., 2000; Ropacki et al., 2007; Stern, 2006; Stern et al., 1996). In a sample of HCV+ patients with cirrhosis or fibrosis who previously evidenced nonresponse to interferon-alpha therapy, individuals with low cognitive reserve evidenced higher rates of cognitive impairment than those with high

cognitive reserve (Bieliauskas et al., 2007). However, similar effects have yet to be confirmed in HCV+ patients without advanced liver disease or with no history of interferon therapy.

A more detailed exploration of potential interactions between cognitive reserve and HCV status is, therefore, warranted but beyond the scope of the present manuscript. We did, however, include *post hoc* analyses, which begin to explore the relationship of our estimate of cognitive reserve (years of education and WRAT3 Reading combined) to neuropsychological outcomes within our sample. There are several reasons why controlling for WRAT3 Reading and/or years of education in between-group analyses raises the potential for an underestimation of group differences and an overestimation of function in our HCV+ groups: (1) Since WRAT3 Reading scores are highly and significantly correlated with years of education, and since we used standardized scores that already corrected for years of education, additional covariate corrections for WRAT3 Reading and years of education likely violate the statistical assumption of multicollinearity. (2) Although WRAT3 Reading scores correlate highly with measures of IQ, it remains an indirect proxy of baseline intellectual ability, confounded by learning disabilities, educational quality, and psychosocial factors that interfere with achievement. These latter factors may, for example, contribute to our HCV+ groups evidencing significantly fewer years of education and lower WRAT3 Reading scores than our HCV− controls, and group differences may not, therefore, reflect differences in baseline IQ. (3) Although studies suggest that reading is less vulnerable to the effects of brain injury and cognitive disorder than many other cognitive domains, reading is not invulnerable to cognitive effects.

Despite these limitations, we used *post hoc* exploratory analyses to examine the extent to which HCV status is associated with cognitive impairment before and after controlling for cognitive reserve. After controlling for cognitive reserve, significant multivariate effects for both the Verbal Memory and Speeded Visual Information Processing domains remained. Furthermore, *post hoc* tests revealed that the HCV+/SUD− group performed significantly worse than HCV− controls on one test of verbal learning (CVLT-II).

CONCLUSIONS

Our overall pattern of results across all primary and *post hoc* analyses was generally consistent and indicates that HCV is associated with cognitive impairment even in the absence of a history of SUD. Our results converge with previous studies and suggest that the most robust HCV-associated cognitive impairments include problems with aspects of verbal learning and reasoning/mental flexibility. These problems are likely not attributable to nonvirological causes such as common medical or psychiatric comorbidities.

Acknowledgments

We would like to thank William Hoffman for his editorial comments and for invaluable professional guidance and scientific mentor-ship over the years; Diane Howieson, Alexander Stevens, and Arthur Vandenbark for their continued mentorship and consultation; Julie Nelligan and Ashlee Whitehead for their initial input in terms of study design and planning; Betsy Zucker, Glen Kenoski, and the other providers within the PVAMC Liver Clinic for their continued collaboration with the Northwest Hepatitis C Resource Center; and Alex Mitchell, Daniel Schwartz, Emily Kizer, Laura Parisi, and Samantha Ruimy for administrative support. This study was supported in part by a Northwest Health Foundation grant and a VA Career Development Award to Dr. Huckans.

REFERENCES

Adair DM, Radkowski M, Jablonska J, Pawelczyk A, Wilkinson J, Rakela J, Laskus T. Differential display analysis of gene expression in brains from hepatitis C-infected patients. AIDS 2005;19 Suppl 3:S145–S150. [PubMed: 16251812]

American Psychiatric Association. Diagnostic and statistical manual for mental disorders. 4th ed.. Washington, DC: American Psychiatric Association; 2000. Text Revision ed.

Beck, AT.; Steer, RA.; Brown, GK. Beck Depression Inventory manual. 2nd ed.. New York: Psychological Corporation; 1996.

Benedict, R. Brief Visuospatial Memory Test—Revised. Lutz, FL: Psychological Assessment Resources, Inc; 1997.

Benton, AL.; Hamsher, KdeS; Sivan, AG. Multilingual Aphasia Examination. Iowa City, IA: AJA Associates; 1989.

Bieliauskas LA, Back-Madruga C, Lindsay KL, Wright EC, Kronfol Z, Lok AS, Fontana RJ. Cognitive reserve and neuropsychological functioning in patients infected with hepatitis C. Journal of the International Neuropsychological Society 2007;13(4):687–692. [PubMed: 17521478]

Bleecker ML, Ford DP, Celio MA, Vaughan CG, & Lindgren KN. Impact of cognitive reserve on the relationship of lead exposure and neurobehavioral performance. Neurology 2007;69(5):470–476. [PubMed: 17664406]

Carey CL, Woods SP, Gonzalez R, Conover E, Marcotte TD, Grant I, Heaton RK. Predictive validity of global deficit scores in detecting neuropsychological impairment in HIV infection. Journal of Clinical and Experimental Neuropsychology 2004;26(3):307–319. [PubMed: 15512922]

Cherner M, Letendre S, Heaton RK, Durelle J, Marquie-Beck J, Gragg B, Grant I. Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine. Neurology 2005;64(8):1343–1347. [PubMed: 15851720]

Collie A. Cognition in liver disease. Liver International 2005;25(1):1–8. [PubMed: 15698392]

Cordoba J, Flavia M, Jacas C, Sauleda S, Esteban JI, Vargas V, Esteban R, Guardia J. Quality of life and cognitive function in hepatitis C at different stages of liver disease. Journal of Hepatol 2003;39(2):231–238.

Delis, D.; Kaplan, E.; Kramer, J. Delis-Kaplan Executive Functioning System. New York, NY: Harcourt Assessment Company; 2001.

Delis, DC.; Kramer, JH.; Kaplan, E.; Ober, BA. California Verbal Learning Test: Adult version manual. San Antonio, TX: The Psychological Corporation; 1987.

Dominitz, JA.; Boyko, EJ.; Koepsell, TD.; Heagert, PJ.; Maynard, C.; Sporleder, JL. Prevalence of hepatitis C infection in veterans: VA Cooperative Study #488. Paper presented at the VA Health Services Research & Development Meeting. Washington, DC: 2004 Mar 4.

Forton DM, Allsop JM, Main J, Foster GR, Thomas HC, Taylor-Robinson SD. Evidence for a cerebral effect of the hepatitis C virus. Lancet 2001;358(9275):38–39. [PubMed: 11454379]

Forton DM, Karayiannis P, Mahmud N, Taylor-Robinson SD, Thomas HC. 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. Journal of Virology 2004;78(10):5170–5183. [PubMed: 15113899]

Forton DM, Taylor-Robinson SD, Thomas HC. Cerebral dysfunction in chronic hepatitis C infection. Journal of Viral Hepatitis 2003;10(2):81–86. [PubMed: 12614463]

Forton DM, Taylor-Robinson SD, Thomas HC. Central nervous system changes in hepatitis C virus infection. European Journal of Gastroenterology and Hepatology 2006;18(4):333–338. [PubMed: 16538103]

Forton DM, Thomas HC, Murphy CA, Allsop JM, Foster GR, Main J, Wesnes KA, Taylor-Robinson SD. Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease. Hepatology 2002;35(2):433–439. [PubMed: 11826420]

Global burden of disease (GBD) for hepatitis C. Journal of Clinical Pharmacology 2004;44(1):20–29. [PubMed: 14681338]

Gossop M, Marsden J, Stewart D. Dual dependence: Assessment of dependence upon alcohol and illicit drugs, and the relationship of alcohol dependence among drug misusers to patterns of drinking, illicit drug use and health problems. Addiction 2002;97(2):169–178. [PubMed: 11860388]

Halstead, WC. Brain and intelligence. Chicago, IL: University of Chicago Press; 1947.

Heaton RK, Grant I, Butters N, White DA, Kirson D, Atkinson JH, McCutchan JA, Taylor MJ, Kelly MD, Ellis RJ, Wolfson T, Velin R, Marcotte TD, Hesselink JR, Jernigan TL, Chandler J, Wallace

M, Abramson I. the HNRC Group. The HNRC 500—Neuropsychology of HIV infection at different disease stages. HIV Neurobehavioral Research Center. Journal of the International Neuropsychological Society 1995;1(3):231–251. [PubMed: 9375218]

Heaton, R.; Miller, W.; Taylor, M.; Grant, I. Revised comprehensive norms for an expanded Halsted-Reitan Battery. Lutz, FL: Psychological Assessment Resources, Inc; 2004.

Hilsabeck RC, Hassanein TI, Carlson MD, Ziegler EA, Perry W. Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C. Journal of the International Neuropsychological Society 2003;9(6):847–854. [PubMed: 14632243]

Hilsabeck RC, Hassanein TI, Ziegler EA, Carlson MD, Perry W. Effect of interferon-alpha on cognitive functioning in patients with chronic hepatitis C. Journal of the International Neuropsychological Society 2005;11(1):16–22. [PubMed: 15686604]

Hilsabeck RC, Perry W, Hassanein TI. Neuropsychological impairment in patients with chronic hepatitis C. Hepatology 2002;35(2):440–446. [PubMed: 11826421]

Huckans MS, Blackwell AD, Harms TA, Hauser P. Hepatitis C disease management patterns in high-risk populations: Testing, infection, and treatment rates among patients with schizophrenia, schizoaffective disorder, and substance use disorders. Psychiatric Services 2006;57(3):403–406. [PubMed: 16525001]

Huckans MS, Blackwell AD, Harms TA, Indest DW, Hauser P. Integrated hepatitis C virus treatment: addressing comorbid substance use disorders and HIV infection. AIDS 2005;19 Suppl 3:S106–S115. [PubMed: 16251805]

Karaivazoglou K, Assimakopoulos K, Thomopoulos K, Theocharis G, Messinis L, Sakellaropoulos G, Labropoulou-Karatza C. Neuropsychological function in Greek patients with chronic hepatitis C. Liver International 2007;27(6):798–805. [PubMed: 17617123]

Klove H. Clinical neuropsychology. Medical Clinics of North America 1963;47:1647–1658. [PubMed: 14078168]

Kraus MR, Schafer A, Wissmann S, Reimer P, Scheurlen M. Neurocognitive changes in patients with hepatitis C receiving interferon alfa-2b and ribavirin. Clinical Pharmacology and Therapeutics 2005;77(1):90–100. [PubMed: 15637534]

Lackner C, Struber G, Liegl B, Leibl S, Ofner P, Bankuti C, Bauer B, Stauber RE. Comparison and validation of simple noninvasive tests for prediction of fibrosis in chronic hepatitis C. Hepatology 2005;41(6):1376–1382. [PubMed: 15915455]

Laskus T, Radkowski M, Adair DM, Wilkinson J, Scheck AC, Rakela J. Emerging evidence of hepatitis C virus neuroinvasion. AIDS 2005;19 Suppl 3:S140–S144. [PubMed: 16251811]

Laskus T, Radkowski M, Bednarska A, Wilkinson J, Adair D, Nowicki M, Nikolopoulou GB, Vargas H, Rakela J. Detection and analysis of hepatitis C virus sequences in cerebrospinal fluid. Journal of Virology 2002;76(19):10064–10068. [PubMed: 12208987]

Letendre SL, Cherner M, Ellis RJ, Marquie-Beck J, Gragg B, Marcotte T, Heaton RK, McCutchan JA, Grant I. The effects of hepatitis C, HIV, and methamphetamine dependence on neuropsychological performance: Biological correlates of disease. AIDS 2005;19 Suppl 3:S72–S78. [PubMed: 16251831]

Lezak, M.; Howieson, D.; Loring, D. Neuropsychological assessment. New York, NY: Oxford University Press; 2005.

Lieb K, Engelbrecht MA, Gut O, Fiebich BL, Bauer J, Jans-sen G, Schaefer M. Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFNalpha): Results from a prospective study. European Psychiatry 2006;21(3):204–210. [PubMed: 16632167]

Loftis JM, Matthews AM, Hauser P. Psychiatric and substance use disorders in individuals with hepatitis C: Epidemiology and management. Drugs 2006;66(2):155–174. [PubMed: 16451091]

Maggi F, Giorgi M, Fornai C, Morrica A, Vatteroni ML, Pistello M, Siciliano G, Nuccorini A, Bendinelli M. Detection and quasispecies analysis of hepatitis C virus in the cerebrospinal fluid of infected patients. Journal of Neurovirology 1999;5(3):319–323. [PubMed: 10414523]

Maier SF. Bi-directional immune-brain communication: Implications for understanding stress, pain, and cognition. Brain, Behavior, and Immunity 2003;17(2):69–85.

Martelli MF, Zasler ND, Bender MC, Nicholson K. Psychological, neuropsychological, and medical considerations in assessment and management of pain. Journal of Head Trauma Rehabilitation 2004;19(1):10–28. [PubMed: 14732828]

Martin EM, Novak RM, Fendrich M, Vassileva J, Gonzalez R, Grbesic S, Nunnally G, Sworowski L. Stroop performance in drug users classified by HIV and hepatitis C virus serostatus. Journal of the International Neuropsychological Society 2004;10(2):298–300. [PubMed: 15012850]

McAndrews MP, Farcnik K, Carlen P, Damyanovich A, Mrkonjic M, Jones S, Heathcote EJ. Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors. Hepatology 2005;41(4):801–808. [PubMed: 15793853]

Michiels V, Cluydts R. Neuropsychological functioning in chronic fatigue syndrome: A review. Acta Psychiatrica Scandinavica 2001;103(2):84–93. [PubMed: 11167310]

Miele GM, Carpenter KM, Cockerham MS, Trautman KD, Blaine J, Hasin DS. Substance Dependence Severity Scale: Reliability and validity for ICD-10 substance use disorders. Addictive Behaviors 2001;26(4):603–612. [PubMed: 11456080]

Mitrushina, M.; Boone, K.; Razani, J.; D'Elia, L. Handbook of normative data for neuropsychological assessment. New York, NY: Oxford University Press, Inc; 2005.

Morsica G, Bernardi MT, Novati R, Uberti Foppa C, Castagna A, Lazzarin A. Detection of hepatitis C virus genomic sequences in the cerebrospinal fluid of HIV-infected patients. Journal of Medical Virology 1997;53(3):252–254. [PubMed: 9365891]

Moselhy HF, Georgiou G, Kahn A. Frontal lobe changes in alcoholism: A review of the literature. Alcohol and Alcoholism 2001;36(5):357–368. [PubMed: 11524299]

Osterrieth PA. Le test de copie d'une figure complexe. Archives de Psychologie 1944;30:206–356. translated by J. Corwin & F.W. Bylsma (1993), *The Clinical Neuropsychologist, 7*, 9–15.

Pereda M, Ayuso-Mateos JL, Gomez Del Barrio A, Echevarria S, Farinas MC, Garcia Palomo D, Gonzalez Macias J, Vazquez-Barquero JL. Factors associated with neuropsychological performance in HIV-seropositive subjects without AIDS. Psychological Medicine 2000;30(1): 205–217. [PubMed: 10722191]

Pfennig A, Littmann E, Bauer M. Neurocognitive impairment and dementia in mood disorders. Journal of Neuropsychiatry and Clinical Neurosciences 2007;19(4):373–382. [PubMed: 18070839]

Porter RJ, Bourke C, Gallagher P. Neuropsychological impairment in major depression: Its nature, origin and clinical significance. The Australian and New Zealand Journal of Psychiatry 2007;41(2):115–128. [PubMed: 17464689]

Radkowski M, Wilkinson J, Nowicki M, Adair D, Vargas H, Ingui C, Rakela J, Laskus T. Search for hepatitis C virus negative-strand RNA sequences and analysis of viral sequences in the central nervous system: Evidence of replication. Journal of Virology 2002;76(2):600–608. [PubMed: 11752151]

Reitan RB. Investigation of the validity of Halstead's measures of biological intelligence. Archives of Neurology and Psychiatry 1955;73:28–35. [PubMed: 13217520]

Reitan, RM.; Wolfson, D. The Halstead-Reitan Neuropsychological Test Battery. Tuscson, AZ: Neuropsychological Press; 1985.

Ropacki SA, Bert AA, Ropacki MT, Rogers BL, Stern RA. The influence of cognitive reserve on neuropsychological functioning following coronary artery bypass grafting (CABG). Archives of Clinical Neuropsychology 2007;22(1):73–85. [PubMed: 17161581]

Rosen WG. Verbal fluency in aging and dementia. Journal of Clinical Neuropsychology 1980;2:135–146.

Seeff LB, Hoofnagle JH. Appendix: The National Institutes of Health Consensus Development Conference management of hepatitis C 2002. Clinics in Liver Disease 2003;7(1):261–287. [PubMed: 12691470]

Silberbogen AK, Janke EA, Hebenstreit C. A closer look at pain and hepatitis C: Preliminary data from a veteran population. Journal of Rehabilitation Research and Development 2007;44(2):231–244. [PubMed: 17551875]

Stern RA, Silva SG, Chaisson N, Evans DL. Influence of cognitive reserve on neuropsychological functioning in asymptomatic human immunodeficiency virus-1 infection. Archives of Neurology 1996;53(2):148–153. [PubMed: 8639064]

Stern Y. Cognitive reserve and Alzheimer disease. Alzheimer Disease and Associated Disorders 2006;20(3 Suppl 2):S69–S74. [PubMed: 16917199]

Taylor MJ, Letendre SL, Schweinsburg BC, Alhassoon OM, Brown GG, Gongvatana A, Grant I. The HNRC. Hepatitis C virus infection is associated with reduced white matter N-acetylaspartate in abstinent methamphetamine users. Journal of the International Neuropsychological Society 2004;10:110–113. [PubMed: 14751013]

Verdejo-Garcia A, Lopez-Torrecillas F, Gimenez CO, Perez-Garcia M. Clinical implications and methodological challenges in the study of the neuropsychological correlates of cannabis, stimulant, and opioid abuse. Neuropsychology Review 2004;14(1):1–41. [PubMed: 15260137]

Vik PW, Cellucci T, Jarchow A, Hedt J. Cognitive impairment in substance abuse. The Psychiatric Clinics of North America 2004;27(1):97–109. ix. [PubMed: 15062633]

von Giesen HJ, Heintges T, Abbasi-Boroudjeni N, Kucukkoylu S, Koller H, Haslinger BA, Oette M, Arendt G. Psychomotor slowing in hepatitis C and HIV infection. Journal of Acquired Immune Deficiency Syndromes 2004;35(2):131–137. [PubMed: 14722444]

Wai CT, Greenson JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, Lok AS. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology 2003;38(2):518–526. [PubMed: 12883497]

Wechsler, D. Wechsler Adult Intelligence Scale, administration and scoring manual, third edition. New York, NY: Psychological Corporation; 1997.

Weissenborn K, Krause J, Bokemeyer M, Hecker H, Schuler A, Ennen JC, Ahl B, Manns MP, Boker KW. Hepatitis C virus infection affects the brain-evidence from psychometric studies and magnetic resonance spectroscopy. Journal of Hepatology 2004;41(5):845–851. [PubMed: 15519659]

Whitehead AJ, Dobscha SK, Morasco BJ, Ruimy S, Bussell C, Hauser P. Pain, substance use disorders and opioid analgesic prescription patterns in veterans with hepatitis C. Journal of Pain Symptom Management 2008;36(1):39–45.

Wilkinson, G. WRAT3 administration manual. DE: Wide Range; 1993.

Wilson CJ, Finch CE, Cohen HJ. Cytokines and cognition—The case for a head-to-toe inflammatory paradigm. Journal of the American Geriatrics Society 2002;50(12):2041–2056. [PubMed: 12473019]

APPENDIX

Table A1

Summary of neuropsychological performance by cognitive domain in published studies comparing HCV+ adults to HCV− controls without liver disease (LD)

	Study groups	Language/ Fluency	Verbal Memory	Visuospatial Memory	Auditory Attention	Speeded Visual Processing	Motor Speed	Visuomotor Construction	Reasonin Mental Flexibili
Forton et al. (2002) (England)	27 HCV+/mild LD 16 HCV−/ HCV cleared	—	?	?	—	Y	—	—	—
Cordoba et al. (2003) (Spain)	40 HCV+/mild LD 40 HCV+/ compensated cirrhosis 40 HCV+/ decompensated cirrhosis 40 HCV−	N	N	—	N	N	N	—	—
Martin et al. (2004) (United States)	20 HCV+/HIV −/SUD+ 28 HCV+/HIV +/SUD+	—	—	—	—	Y	—	—	—

	Study groups	Language/ Fluency	Verbal Memory	Visuospatial Memory	Auditory Attention	Speeded Visual Processing	Motor Speed	Visuomotor Construction	Reasonin Mental Flexibili
	39 HCV−/HIV +/SUD+ 69 HCV−/HIV −/SUD+								
von Giesen et al. (2004) (Germany)	44 HIV−/HCV + 43 HIV+/HCV − 43 HIV+/HCV + 98 HIV−/HCV −	—	—	—	—	—	Y	—	—
Weissenborn et al. (2004) (Germany)	15 HCV+/mild fatigue 15 HCV+/ moderate fatigue 15 HCV−	—	Y	Y?	N	Y	—	N	Y
McAndrews et al. (2005) (Canada)	37 HCV+ 46 HCV−	—	Y	N	N	N	—	—	—
Cherner et al. (2005)/ Letendre et al. (2005) (United States)	2 HCV+/HIV −/Meth− 33 HCV+/HIV −/Meth+ 8 HCV+/HIV +/Meth− 40 HCV+/HIV +/Meth+ 83 HCV−/HIV −/Meth+ 105 HCV−/ HIV+/Meth− 69 HCV−/HIV +/Meth+ 90 HCV−/HIV −/Meth−	N	Y	Y	N	N	Y	—	Y
Karaivazoglou et al. (2007) (Greece)	32 HCV+ 20 HCV− 29 HBV+	N	Y	—	—	N	—	—	—
Huckans et al. (2008) (United States)	24 HCV+/ SUD− 39 HCV+/ SUD+ 56 HCV−/ SUD−	N	Y	N	Y	Y	N	N	Y

Note. Y = Compared with HCV− controls, HCV+ patients were found to perform worse on cognitive tests. N = HCV+ patients did not perform worse than HCV− controls on cognitive tests. — = Cognitive domain was not measured directly. ? = It is unclear from the published manuscript whether tests within this cognitive domain were used. LD = liver disease; Meth = recent methamphetamine abuse; SUD = history of substance use disorder.

Table A2

Subtests by cognitive domain and the source of their respective normative samples

	Norms	Type of standard score
Language		
Letter Fluency—COWA (Benton et al., 1989)	D-KEFS manual (Delis et al., 2001)[A]	Scaled score
Category Fluency—Animals (Rosen, 1980)	Lezak et al. (2005)[A]	*z* Score

	Norms	Type of standard score
Verbal Memory		
CVLT-II	CVLT-II manual/computer printout (Delis et al., 1987)[A,G]	Total Immediate Recall: *t* score Long Delay Free Recall: *z* score Recognition Correct Hits: *z* score
Visuospatial Memory		
BVMT-R	BVMT-R manual (Benedict, 1997)[A]	*t* Score
RCF Immediate and Delayed Recall (Osterrieth, 1944)	Mitrushina et al. (2005)[A]	*z* Score
Auditory Attention		
WAIS-III Digit Span	WAIS-III manual (Wechsler, 1997)[A]	Scaled score
WAIS-III Letter Number Sequencing	WAIS-III manual (Wechsler, 1997)[A]	Scaled score
Speeded Visual Information Processing/Attention		
Trails A and B (Reitan & Wolfson, 1985)	Revised Heaton norms (Heaton et al., 2004)[A,E,G,R]	*t* Score
WAIS-III Digit Symbol	WAIS-III manual (Wechsler, 1997)[A]	Scaled score
D-KEFS CWIT	D-KEFS manual (Delis et al., 2001)[A]	Scaled score
Motor Speed		
Finger Tapping (Halstead, 1947; Reitan, 1955)	Revised Heaton norms (Heaton et al., 2004)[A,E,G,R]	*t* Score
Grooved Pegboard (Klove, 1963)	Revised Heaton norms (Heaton et al., 2004)[A,E,G,R]	*t* Score
Visuomotor Construction		
RCF Copy (Osterrieth, 1944)	Mitrushina et al. (2005)[A]	*z* Score
Reasoning/Mental Flexibility		
D-KEFS Sorting	D-KEFS manual (Delis et al., 2001)[A]	Scaled score
D-KEFS Proverbs	D-KEFS manual (Delis et al., 2001)[A]	Scaled score
WAIS-III Matrix Reasoning	WAIS-III manual (Wechsler, 1997)[A]	Scaled score

Note. BVMT-R = Brief Visuospatial Memory Test, revised; COWA = Controlled Oral Word Association; CVLT-II = California Verbal Learning Test, second edition; CWIT = Color–Word Interference Test; D-KEFS = Delis-Kaplin Executive Functioning System; RCF = Rey Complex Figure; WAIS-III = Wechsler Adult Intelligence Scale, third edition. Superscripts indicate that norms correct for the following demographic factors: A = age, E = years of education, G = gender, R = race/ethnicity.

Table 1

Demographic and clinical characteristics by study group

	Total sample	HCV−/SUD−	HCV+/SUD−	HCV+/SUD+	*p* Value
Total *N*	119	56	24	39	
Demographics					
Age (mean years ± *SD*)	53.81 ± 8.55	54.02 ± 11.41	53.04 ± 5.55	53.97 ± 4.42	.888
Male gender	106 (89.1%)	46 (82.1%)[a]	21 (87.5%)[b]	39 (100.0%)[ab]	.023
Caucasian	109 (91.6%)	52 (92.9%)	21 (87.5%)	36 (92.3%)	.719
Years of education (mean ± *SD*)	14.55 ± 2.38	15.71 ± 2.68[ab]	13.92 ± 1.67[a]	13.26 ± 1.23[b]	<.001
Psychiatric history					
Current psychiatric diagnosis	55 (46.2%)	24 (42.9%)	9 (37.5%)	22 (56.4%)	.273
Mood disorder	46 (38.7%)	21 (37.5%)	8 (33.3%)	17 (43.6%)	.700
PTSD	22 (18.5%)	10 (17.9%)	5 (20.8%)	7 (17.9%)	.947
Other anxiety disorder	18 (15.1%)	9 (16.1%)	3 (12.5%)	6 (15.4%)	.919
Medical history					
Current medical diagnosis	65 (54.6%)	33 (58.9%)	13 (54.2%)	19 (48.7%)	.618
Diabetes	18 (15.1%)	12 (21.4%)	1 (4.2%)	5 (12.8%)	.128
Hyperlipidemia	27 (22.7%)	17 (30.4%)	3 (12.5%)	7 (17.9%)	.152
Hypertension	35 (29.4%)	20 (35.7%)	9 (37.5%)	6 (15.4%)	.065
Cardiovascular disease	12 (10.1%)	7 (12.5%)	2 (8.3%)	3 (7.7%)	.711
Asthma/pulmonary	16 (13.4%)	5 (8.9%)	4 (16.7%)	7 (17.9%)	.395
Kidney dysfunction	2 (1.7%)	1 (1.8%)	0 (0.0%)	1 (2.6%)	.743
Thyroid dysfunction	7 (5.9%)	3 (5.4%)	1 (4.2%)	3 (7.7%)	.826

Note. Data expressed as *n*, with (%) in terms of *n* over total *N* unless otherwise stated. Variables with the same superscript yielded significant univariate effects ($p \leq .05$) using *post hoc* Scheffe tests. HCV = infected with chronic hepatitis C virus; PTSD = posttraumatic stress disorder; *SD* = standard deviation; SUD = history of substance use disorder, currently in remission.

Table 2

Neuropsychological performance by study group and cognitive domain

	Total sample[1]	HCV−/SUD−[2]	HCV+/SUD−[2]	HCV+/SUD+[2]	Partial Eta[2]	*p* Value
Language	Wilks' Λ = .95, $F(4, 230) = 1.635$, $p = .166$				.028	
Letter Fluency	10.20 ± 3.31	10.70 ± 0.45	10.58 ± 0.69	9.33 ± 0.54	.034	.137
Category Fluency	0.04 ± 1.03	0.20 ± 0.14	−0.19 ± 0.21	−0.06 ± 0.17	.024	.245
Verbal Memory	Wilks' Λ = .86, $F(6, 228) = 2.95$, $p = .009$				.083	
CVLT-II Total Immediate Recall	47.93 ± 10.78	51.96 ± 1.41[ab]	43.63 ± 2.15[a]	44.67 ± 1.69[b]	.121	.001
CVLT-II Long Delay Free Recall	−0.12 ± 0.88	0.04 ± 0.12	−0.46 ± 0.18	−0.19 ± 0.14	.045	.067
CVLT-II Recognition Correct Hits	−0.46 ± 1.23	−0.31 ± 0.17	−0.77 ± 0.26	−0.68 ± 0.20	.026	.214
Visuospatial Memory	Wilks' Λ = .914, $F(8, 194) = 1.12$, $p = .351$				.044	
BVMT-R Total Immediate Recall	39.39 ± 10.72	42.93 ± 1.43	36.61 ± 2.44	37.72 ± 1.83	.071	.025
BVMT-R Delayed Recall	44.72 ± 13.04	47.79 ± 1.76	41.89 ± 3.02	43.28 ± 2.26	.039	.135
RCF Immediate Recall	−0.27 ± 0.82	−0.12 ± 0.12	−0.42 ± 0.20	−0.38 ± 0.15	.028	.242
RCF Delayed Recall	−0.31 ± 0.83	−0.18 ± 0.12	−0.42 ± 0.20	−0.45 ± 0.15	.025	.287
Auditory Attention	Wilks' Λ = .893, $F(4, 230) = 3.33$, $p = .011$				.055	
WAIS-III Digit Span	10.30 ± 2.73	11.96 ± 0.36[a]	9.04 ± 0.55[a]	10.08 ± 0.43	.091	.004
WAIS-III Letter Number Sequencing	10.56 ± 2.75	11.37 ± 0.36[a]	9.71 ± 0.54[a]	10.28 ± 0.43	.064	.022
Speeded Visual Information Processing/Attention	Wilks' Λ = .753, $F(10, 208) = 3.17$, $p = .001$				.132	
Trail A	45.64 ± 9.84	46.06 ± 1.40	44.85 ± 2.28	44.42 ±1.66	.008	.636
Trail B	46.73 ± 9.09	48.47 ± 1.27	44.75 ± 2.06	45.82 ± 1.50	.028	.211
WAIS-III Digit Symbol	8.97 ± 2.73	10.17 ± 0.35[a]	9.05 ± 0.58	7.68 ± 0.42[a]	.161	.000
D-KEFS CWIT Inhibition	9.64 ± 3.18	10.13 ± 0.44	8.75 ± 0.72	9.55 ± 0.52	.025	.249
D-KEFS CWIT Switching	10.51 ± 2.69	11.0 ± 0.36	10.80 ± 0.59	10.00 ± 0.42	.030	.192
Motor Speed	Wilks' Λ = .944, $F(8, 204) = .749$, $p = .648$				.029	
Finger Tapping Dominant	39.59 ± 8.49	40.20 ± 1.21	39.10 ± 1.88	37.53 ± 1.44	.019	.368
Finger Tapping Nondominant	43.29 ± 9.50	43.06 ± 1.33	44.14 ± 2.10	44.08 ± 1.58	.003	.849
Pegboard Dominant	42.93 ± 9.74	45.38 ± 2.17	42.28 ± 1.39	45.81 ± 1.65	.014	.477
Pegboard Nondominant	43.45 ± 9.17	44.72 ± 2.04	43.51 ± 1.31	44.14 ± 1.56	.003	.874
Visuomotor Construction						

	Total sample[1]	HCV−/SUD−[2]	HCV+/SUD−[2]	HCV+/SUD+[2]	Partial Eta[2]	*p* Value
RCF Copy	−0.67 ± 1.28	−0.63 ± 0.17	−0.81 ± 0.26	−0.51 ± 0.21	.007	.661
Reasoning/Mental Flexibility	Wilks' Λ = .817, $F(6, 228) = 4.03$, $p = .001$				.096	
D-KEFS Sorting Correct Sorts	9.69 ± 2.69	10.73 ± 0.35[ab]	8.87 ± 0.53[a]	8.56 ± 0.41[b]	.140	.000
D-KEFS Proverbs Free Inquiry	9.34 ± 2.75	10.09 ± 0.37[a]	9.17 ± 0.56	8.23 ± 0.44[a]	.084	.006
WAIS-III Matrix Reasoning	11.43 ± 2.82	12.27 ± 0.37[ab]	10.50 ± 0.57[a]	10.64 ± 0.45[b]	.088	.005

Note. Variables with the same superscript yielded significant univariate effects ($p \leq .05$) using *post hoc* Scheffe tests. BVMT-R = Brief Visuospatial Memory Test, revised; CVLT-II = California Verbal Learning Test, second edition; CWIT = Color–Word Interference Test; D-KEFS = Delis-Kaplin Executive Functioning System; HCV = currently infected with chronic hepatits C virus; RCF = Rey Complex Figure; SUD = history of substance use disorder, currently in remission; WAIS-III = Wechsler Adult Intelligence Scale, third edition.

[1] Data expressed as the mean ± standard deviation.

[2] Data expressed as estimated marginal means ± standard error.

Table 3

Proportion of global and domain-specific cognitive impairment among groups

	Total sample	HCV−/SUD−	HCV+/SUD−	HCV+/SUD+	*p* Value
Total *N*	119	56	24	39	—
Language Fluency	27 (22.7%)	10 (17.9%)	6 (25.0%)	11 (28.2%)	.477
Verbal Memory	32 (26.9%)	9 (16.1%)	10 (41.7%)	13 (33.3%)	.034
Visuospatial Memory	46 (38.7%)	18 (32.1%)	11 (45.8%)	17 (43.6%)	.385
Auditory Attention	14 (11.8%)	5 (8.9%)	4 (16.7%)	5 (12.8%)	.600
Speeded Visual Information Processing/Attention	32 (26.9%)	12 (10.1%)	2 (8.3%)	11 (28.2%)	.172
Motor Speed	67 (56.3%)	30 (53.6%)	12 (50.0%)	25 (64.1%)	.470
Visuomotor Construction	36 (30.3%)	17 (30.4%)	9 (37.5%)	10 (25.6%)	.612
Reasoning/Mental Flexibility	23 (19.3%)	3 (5.4%)	6 (25.0%)	8 (20.5%)	.029
Global deficit score	32 (26.9%)	13 (23.2%)	9 (37.5%)	15 (38.5%)	.218

Note. Data expressed as *n*, with (%) in terms of *n* over total *N*. HCV = infected with chronic hepatitis C virus; SUD = history of substance use disorder, currently in remission.

Table 4

Average total deficit score by cognitive domain

	Total sample	HCV−/SUD−	HCV+/SUD−	HCV+/SUD+
Total *N*	119	56	24	39
Language Fluency	0.20 ± 0.45	0.14 ± 0.33	0.23 ± 0.55	0.27 ± 0.52
Verbal Memory	0.38 ± 0.63	0.22 ± 0.49	0.58 ± 0.76	0.48 ± 0.67
Visuospatial Memory	0.57 ± 0.81	0.48 ± 0.76	0.74 ± 0.87	0.60 ± 0.83
Auditory Attention	0.11 ± 0.33	0.10 ± 0.36	0.17 ± 0.41	0.08 ± 0.22
Speeded Visual Information Processing/Attention	0.34 ± 0.56	0.34 ± 0.54	0.17 ± 0.44	0.45 ± 0.64
Motor Speed	0.66 ± 0.67	0.63 ± 0.71	0.59 ± 0.57	0.75 ± 0.66
Visuomotor Construction	0.64 ± 1.16	0.64 ± 1.17	0.79 ± 1.28	0.54 ± 1.10
Reasoning/Mental Flexibility	0.23 ± 0.41	0.16 ± 0.37	0.27 ± 0.44	0.30 ± 0.45
Global deficit score	0.39 ± 0.34	0.33 ± 0.34	0.43 ± 0.29	0.45 ± 0.36

Note. Data expressed as mean total deficit score ± standard deviation. HCV = infected with chronic hepatitis C virus; SUD = history of substance use disorder, currently in remission.

Table 5

Estimated cognitive reserve, current depressive symptom severity, and current pain rating by group

	Total sample	HCV−/SUD−	HCV+/SUD−	HCV+/SUD+	*p* Value
Total *N*	119	56	24	39	—
Estimated cognitive reserve					
WRAT3 Reading	102.1 ± 11.20	107.20 ± 9.20[ab]	99.21 ± 10.79[a]	96.64 ± 11.18[b]	<.001
Current depressive symptom severity					
BDI-II Total	9.71 ± 10.19	6.46 ± 7.18[a]	11.54 ± 12.24	13.26 ± 11.25[a]	.003
Current pain rating					
Self rating 1–10	2.76 ± 2.60	1.80 ± 2.27[ab]	3.38 ± 2.93[a]	3.77 ± 2.38[b]	<.001

Note. Data expressed as the mean ± standard deviation. Variables with the same superscript were significantly different ($p \leq .05$) using *post hoc* Scheffe tests. BDI-II = Beck Depression Inventory-second edition; HCV = infected with chronic hepatitis C virus; SUD = history of substance use disorder, currently in remission; WRAT = Wide Range Achievement Test, third edition.

Table 6

p Values from multivariate and univariate tests comparing three study groups (HCV–/SUD–, HCV+/SUD–, and HCV+/SUD+) on neuropsychological performance, with estimated cognitive reserve, current depressive symptom severity, and current pain ratings entered as covariates

Covariates	Estimated cognitive reserve[1]	Current depressive symptom severity [2]	Current pain rating[3]
Verbal Memory	.048	.018	.053[P]
CVLT-II Total Immediate	.029	.005	.016[P]
CVLT-II Long Delay Free Recall	.165	.144	.196
CVLT-II Recognition Correct Hits	.057[E]	.510[D]	.516
Auditory Attention	.163[W]	.036	.047
WAIS-III Digit Span	.076[W]	.012	.010
WAIS-III Letter Number Sequencing	.171[W]	.057	.128[P]
Speeded Visual Information	.002[W]	.001	.004
Processing/Attention			
Trails A	.177	.511	.414
Trails B	.219[EW]	.205	.282
WAIS-III Digit Symbol	.000	.000	.000
D-KEFS CWIT Inhibition	474[W]	.334	.389
D-KEFS CWIT Switching	.643[W]	.340	.547[P]
Reasoning/Mental Flexibility	.181[W]	.011[D]	.017[P]
D-KEFS Sorting Correct Sorts	.061	.005[D]	.003
D-KEFS Proverbs Free Inquiry	.649[EW]	.018	.033
WAIS-III Matrix Reasoning	.178[W]	.017	.087[P]

Note. *p* Values are displayed for each test controlling for covariates. Rows with cognitive domain names include multivariate effects (Wilks Λ, MANCOVAs), with the three study groups and covariates entered as independent variables and standardized scores for each relevant subtest within a cognitive domain entered as multiple dependent variables. Rows with subtest names include univariate effects (*F* tests), with the three study groups and covariates entered as independent variables and individual subtests entered as dependent variables. Covariates with *p* values of <.05 are indicated by D = depression, W = WRAT3, E = education, and P = pain. CWIT = Color–Word Interference Test.

[1] Cognitive reserve was estimated using years of education and standard scores on WRAT3 Reading.

[2] Depression was measured using the Beck Depression Inventory, second edition.

[3] Pain was measured with a single-item self-rating of current pain on a Likert scale of 1–10, from minimal to severe.