# Neurocognitive Effects of the Hepatitis C Virus

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Evidence is increasing that the hepatitis C virus (HCV) is neurovirulent. Neuroimaging studies suggest that individuals with HCV infection show alterations in the structure and function of several neural systems, most notably the frontostriatal circuits. Several studies also demonstrated evidence of cognitive impairment across a variety of ability areas in about 30% to 40% of HCV-infected individuals. Although certain comorbidities (eg, substance abuse, HIV coinfection, neuropsychiatric symptoms) may increase the risk of neurocognitive deficits in HCV-positive individuals, it appears that neurocognitive impairment is present in HCV-positive individuals without significant comorbidities. We provide an overview of the neurocognitive effects of HCV infection and present empirical evidence examining episodic memory abilities in HCV-positive individuals. The results of our study indicate that HCV-positive individuals have difficulties learning new verbal and visual information, but are nevertheless able to retain and recognize the information they have learned. Implications for everyday functioning are discussed.

## Introduction

It is estimated that about one third of people with chronic hepatitis C virus (HCV) infection experience neurocognitive impairments, which can be independent of the severity of liver disease, hepatic encephalopathy, viral load and genotype, and comorbid drug abuse [1,2]. In this article, we review relevant evidence supporting neurovirulence, specific brain systems affected, comorbidities (eg, substance abuse, HIV-coinfection, neuropsychiatric factors), HCV treatment effects, commonly affected neuropsychologic domains, and implications for daily living. We also report novel preliminary data regarding the profile of HCV-associated deficits in learning and memory.

## Neurovirulence of HCV

Evidence is increasing that HCV is neurovirulent. The exact mechanism by which HCV enters the central nervous system is unknown; however, it was postulated that HCV may cross the blood–brain barrier via infected monocytes using a Trojan horse mechanism [3]. The hypothesis that HCV can cause brain dysfunction is supported by replication of HCV in the astroglia of patients with AIDS [4], detection of HCV RNA in brain tissue [5], and demonstration of metabolic changes resembling HIV infection [6]. A study showed that among HCV/HIV coinfected persons, immunoreactivity occurred in the astroglia of white matter and (to a lesser extent) in macrophages and microglia [7], whereas another study detected HCV RNA primarily in microglia and macrophages and to a lesser degree in astrocytes [8]. It remains unclear if neurocognitive and neuropsychiatric symptoms of HCV-infected individuals relate to the direct effects of HCV infection on the brain or to a nonspecific reaction of brain cells to mediators of inflammation (eg, cytokines) [3].

## Brain Systems Affected in HCV

Neuroimaging studies suggest that HCV-positive individuals show altered structure and function of several neuronal systems, including the frontal neocortex, basal ganglia, and connecting white matter tracts [6,9]. Magnetic resonance spectroscopy (MRS) studies usually measure four compounds thought to be the most reliable: N-acetylaspartate (NAA), a marker of neuronal integrity; choline (Cho), a measure of cell membrane turnover and lipid changes; myo-Inositol (Ins), a possible indicator of glial proliferation and/or osmolar changes; and creatine (Cr), an indicator of high-energy stores that is often used as a relative standard for other metabolites [10].

Similar to findings in HIV disease, higher Cho/Cr ratios are found in the white matter and the basal ganglia of HCV-positive individuals compared with healthy

volunteers, suggesting that HCV infects the brain directly, activates microglia via peripherally derived cytokines, or both [6]. MRS studies also found elevated metabolic markers of neuronal injury and neuroinflammation in the basal ganglia and frontal white matter of persons with HCV [11]. Reductions in the NAA/Cr ratio in the frontal gray matter were demonstrated in HCV-infected patients, but no changes were observed for the Cho/Cr ratio [9]. Furthermore, increased Cho and decreased NAA were demonstrated in the white matter of HCV-positive patients compared with seronegative subjects [12]. Most recently, Forton et al. [13] found a significant increase in the Ins/Cr ratio in a group of HCV-positive individuals with mild liver disease compared with healthy adults.

Using single photon emission tomography, alterations of mesencephalic/hypothalamic serotonin and striatal dopamine transporter binding were observed in some HCV-positive patients [14]. A study using positron emission tomography showed decreased glucose metabolism in the limbic association cortex of HCV-positive patients compared with healthy adults [15]. Future studies of brain functioning in HCV-infected individuals would benefit from examining the integrity of white matter tracts using diffusion tensor imaging. Also, structural MRI would provide information regarding volumes of gray and white matter overall, volumes of specific regions (eg, basal ganglia structures, hippocampus), and volume of abnormal white matter that may reflect foci of HCV-induced inflammation. Finally, functional MRI studies would shed light on the brain activity of HCV-positive persons while performing cognitive tasks. Other possibilities include studies of cortical thickness, which appears to be reduced in other infectious diseases (eg, HIV [16]), and multimodal approaches [17].

## Cognitive Dysfunction in HCV

Consistent with the brain imaging data, several studies also demonstrated evidence of cognitive impairment across a variety of ability areas among HCV-positive individuals [3]. However, the severity of impairment and the specific cognitive domains affected vary somewhat across the literature [18]. Notably, the pattern of cognitive deficits reported among individuals infected with HCV may be influenced by the severity of liver disease (eg, liver fibrosis, decompensated cirrhosis), other comorbidities (eg, substance use disorders, HIV infection, neuropsychiatric symptoms), and whether the HCV-positive individual has initiated treatment for HCV (Table 1).

### Severity of liver disease

HCV causes a fluctuating chronic hepatitis that may progress to cirrhosis, hepatocellular carcinoma, and ultimately, liver failure. It is well established that advanced forms of liver disease are accompanied by overt and global cognitive deficits (ie, hepatic encephalopathy [19]). Hepatic encephalopathy symptoms include altered level of consciousness, asterixis, spatial disorientation, and visual hallucinations. Nevertheless, HCV-associated neurocognitive impairment also was found among HCV-positive individuals without marked liver disease, in the absence of hepatic encephalopathy. This is not to suggest that more advanced liver disease does not worsen neurocognitive impairment. For instance, a study by Hilsabeck et al. [20] showed greater cognitive dysfunction in those with greater fibrosis stage, but similar cognitive performance between individuals with and without cirrhosis. In the context of chronic HCV infection, comparing individuals who had cirrhosis without decompensation with those who had cirrhosis with prior decompensations revealed that those with decompensated cirrhosis were impaired in the domains of attention, executive function, and motor skills, whereas individuals without cirrhosis and those with mild chronic HCV performed similarly within normal levels [21]. Importantly, several studies found cognitive impairment in HCV-positive individuals without severe liver disease [6,12].

### Substance use disorders

The prevalence of substance use disorders among HCV-infected individuals is high, and intravenous drug use (IVDU) is the primary risk factor for chronic HCV infection (eg, 60%–70% of persons with chronic HCV infection indicate a history of IVDU). Few studies have assessed the effect of substance abuse on cognitive functioning in chronic HCV, and the most notable have found little [22•] to no [23] significant differences between HCV-positive individuals with and without history of substance use disorders.

### HIV coinfection

Because viral transmission routes overlap somewhat (eg, IVDU), many HCV-positive individuals are also HIV-infected. Coinfected individuals show impairment on measures of executive function, psychomotor speed, and global cognitive function [24–26]. In a recent study comparing coinfected individuals with HIV-monoinfected individuals, coinfected individuals were more likely to be classified as neuropsychologically impaired and had particular impairments in learning and recall [27].

### Neuropsychiatric symptoms

High levels of general psychologic distress and self-reported mood disturbance appear prevalent among HCV-positive individuals [28]. Fatigue is the most frequently reported symptom, with prevalence estimates ranging from 53% to 70% [29]. Approximately 28% to 50% of HCV-infected individuals report elevated symptoms of depression, whereas symptoms of anxiety are present in 18% to 41% of the population [30]. Examples of reported associations between neuropsychiatric symptoms and cognition include self-reported depressive symptoms with sustained attention, and moderate fatigue with general slowing on

**Table 1. Selected studies of cognitive dysfunction in individuals with chronic hepatitis C**

| Study | Sample | Findings |
|---|---|---|
| Forton et al. [11] | 27 $HCV^+$ (13 IVDU), 16 cleared HCV (8 IVDU), and 29 HC. | $HCV^+$ uncleared had worse concentration and psychomotor speed. No differences in working memory and attention. |
| Kramer et al. [23] | 100 $HCV^+$ (25 cirrhotic) and 100 $HCV^-$. Other comorbidities: IDVU (23 $HCV^+$). | 16% of $HCV^+$ individuals had abnormal P300 latencies (measure of overall cognitive functioning). No association with disease stage. |
| Hilsabeck et al. [20] | 44 $HCV^+$ without medical comorbidities, 22 $HCV^+$ with medical comorbidities, 14 $HCV^-$ with other liver diseases. Fibrosis stage: mild (15), moderate (4), severe (13), cirrhosis (34). Comorbidities included alcohol hepatitis (10), HIV (8). Other liver disease included HBV (5), cryptogenetic (4). | Deficits in attention, learning, psychomotor speed, and mental flexibility. Visuoconstruction and recall normal. Greater impairment was associated with greater fibrosis stage. $HCV^+$ and $HCV^-$ with other liver diseases performed similarly. |
| Hilsabeck et al. [31] | 21 chronic $HCV^+$ (7 cirrhotic). Other comorbidities: HIV (2), type 2 diabetes (3), alcoholic hepatitis (4), HCV antiviral therapy (5), IVDU (15). | Impairment in visuoconstruction abilities, learning, recall, complex attention, and psychomotor speed. |
| Cordoba et al. [21] | 40 $HCV^+$ mild, 40 $HCV^+$ with compensated cirrhosis, 40 $HCV^+$ with decompensated cirrhosis, and 40 HC. Other comorbidities: arterial hypertension (11), type 2 diabetes (14), IDVU (3). | Decompensated cirrhotic were significantly more impaired on attention, executive function, and motor abilities than other 3 groups. No impairment on learning, recall, or visuoperceptive functioning. |
| Weissenborn et al. [9] | 30 $HCV^+$ (15 with mild fatigue, 15 with moderate fatigue), 15 HC. | Moderately fatigued patients performed significantly worse on attention, learning, and executive function. Recall and visuoconstruction abilities appear to remain intact. |
| Fontana et al. [18] | 201 $HCV^+$ (76 cirrhotic). Comorbidities: IDVU (92), alcohol use disorder (104), drug use disorder (78), lifetime depressive disorder (30), lifetime anxiety disorder (22), type 2 diabetes (50), hypertension (56). | 33% of subjects had evidence of impairment on verbal recall and working memory. Normal on psychomotor speed, executive function, and verbal fluency. Impairment not related to liver fibrosis. |
| McAndrews et al. [12] | 37 $HCV^+$ (11 endorsed depressive symptoms), 42 HC. Fibrosis stage: mild (9), moderate (17), severe (11), cirrhosis (0). | $HCV^+$ individuals have deficits on learning, attention, recall, psychomotor speed. Mental flexibility appeared intact. |
| Bieliauskas et al. [40] | 100 $HVC^+$ with advanced liver fibrosis and nonresponders to interferon therapy (33 cirrhotic). No comorbidities reported. | 44% of subjects categorized as impaired. Learning, recall, and executive function were most affected domains, whereas motor skills and verbal fluency were less affected. |
| Fontana et al. [37•] | 177 $HCV^+$ with advanced liver fibrosis and nonresponders to interferon therapy (65 cirrhotic). Other comorbidities: type 2 diabetes (44). | 32% of subjects were cognitively impaired at baseline. Deficits in verbal recall and working memory. Psychomotor speed, visuomotor tracking, verbal fluency, and executive functioning intact. |
| Karaivazoglou et al. [41•] | 32 $HCV^+$ (7 cirrhotic), 29 $HBV^+$ (6 cirrhotic), 20 HC. | $HCV^+$ worse than HC on verbal learning and recall. $HCV^+$ and $HBV^+$ similarly impaired. Psychomotor speed, verbal fluency, and attention appeared intact. In $HCV^+$, cognitive dysfunction was associated with severity of liver disease. |
| Forton et al. [13] | 16 $HCV^+$ with mild liver disease (10 IDVU). 16 HC. | Significant correlations between elevated myo-inositol/creatine and longer working memory reaction times. |
| Huckans et al. [22•] | 39 $HCV^+$ ($SUD^+$), 24 $HCV^+$ ($SUD^-$), 56 HC. Other comorbidities: mood disorder (25), posttraumatic stress disorder (12), type 2 diabetes (9), hypertension (18). | $HCV^+/SUD^-$ worse than HC on learning, attention, and mental flexibility but only $HCV^+/SUD^+$ worse than HC on psychomotor speed. Verbal fluency, motor skills, and visuomotor abilities intact. |

HBV—hepatitis B virus; HC—healthy controls; HCV—hepatitis C virus; IVDU—intravenous drug use; SUD—substance use disorder.

electroencephalogram [9,11]. In contrast, other studies have not found differences in neuropsychologic performance between HCV-positive individuals with high and low levels of self-reported neuropsychiatric disturbance, or have demonstrated a relationship between fatigue and general cognitive functioning [31,32]. Thus, neuropsychiatric symptoms among HCV-positive individuals may contribute to neurocognitive dysfunction; however, it appears unlikely that neuropsychiatric symptoms alone account for the neurocognitive deficits associated with HCV.

### HCV treatment

Treatment of HCV with pegylated interferon-α and ribavirin was hypothesized to induce neurocognitive impairment, based on research showing a marked increase in neuropsychiatric complaints during treatment [33]. However, self-reported cognitive complaints do not relate strongly to objective, performance-based deficits in neuropsychologic functioning [34]. Indeed, research regarding objective cognitive declines during antiviral treatment produced mixed results, perhaps from variability in study design, duration of follow-up, and outcome measures. Despite these limitations, our review of literature suggests that mild objective impairments may emerge during the first few months of therapy, but appear transient in nature and tend to normalize by 24 weeks [35,36]. In the largest and most comprehensive study, no significant cognitive declines were observed in 177 HCV-positive patients on treatment for 24 weeks, 57 of whom were followed as long as 48 weeks [37•]. Other groups report mild, long-term improvements in cognitive function in individuals who achieve sustained viral response [38]. Considering these data, it may be argued that the possibility of mild, transient declines in some aspects of cognitive functioning associated with treatment does not outweigh the considerable health and quality-of-life benefits of successful antiviral therapy.

## Neurocognitive Impairment by Domain

### Attention

*Attention* refers to several different capacities or processes related to how an individual becomes receptive to stimuli and how he or she may process or focus on such information [39]. Many subcomponent attentional processes exist; some of the most frequently studied aspects are focused attention (ie, ability to respond to a specific stimulus presented on a particular sensory modality), sustained attention/vigilance (ie, capacity to maintain attention to a specific stimulus over time), selective attention (ie, capacity to maintain attention in the face of distracting or competing stimuli), and divided attention (ie, ability to respond simultaneously to multiple tasks) [39]. The most striking study of attention deficits in HCV infection showed that up to 82% of HCV-positive individuals with other medical comorbidities had impaired performance on tests of sustained attention, and 59% showed impairment on tests of selective attention, whereas 49% of HCV-positive individuals without other medical comorbidities had impairment on sustained attention and 25% had impairment on selective attention [20]. In a similar HCV-positive group studied using slightly different methods, 38% of individuals were impaired on selective attention [31]. Another study found selective attention deficits only in HCV-positive individuals with decompensated cirrhosis [21]. However, other studies found attention deficits in individuals with mild HCV infection and no comorbidities, including difficulties with focused and divided attention, sustained attention, and selective auditory attention [9, 13,22•].

### Psychomotor speed

*Psychomotor speed* refers to the amount of time it takes a person to process a signal, prepare a response, and execute that response [39]. It is a broad, often amorphous, construct that is closely related to attention, because slowed processing speed sometimes underlies attentional deficits [39]. Several studies assessed this domain in HCV and the results are somewhat mixed: some studies show psychomotor speed to be intact among HCV-positive individuals [9,12,18,21], whereas others suggest that psychomotor speed is one of the most affected neurocognitive domains [11,20,31]. In one study, 25% of HCV-positive individuals and 41% of HCV-positive individuals with other comorbidities were impaired on a basic processing-speed measure (ie, Trial Making Test, part A) [20]. Impairments in this domain may be particularly susceptible to comorbidities (eg, substance dependence and chronic medical conditions) [20,22•].

### Executive function

*Executive functions* encompass a broad range of "higher-order" abilities including those responsible for planning, mental flexibility, abstract reasoning, concept formation, initiating appropriate actions, and inhibiting inappropriate actions. About 30% of HCV-positive individuals were impaired on a test of mental flexibility, abstract reasoning, and concept formation [40]. Similarly, some studies found that HCV-positive persons had deficits in verbal response inhibition, reasoning, and mental flexibility [21,22•]. Other studies found these abilities intact among HCV-positive individuals [12,18,37•].

One aspect of executive function that is sometimes considered an independent domain is verbal fluency, which is the ability to rapidly produce words, in speech or writing, within a certain time. Among HCV-positive individuals, only one study found minor impairment, whereas four other studies found this domain intact in individuals with HCV infection [18,21,37•,41•]. Cordoba et al. [21] found verbal fluency impairments among HCV-positive individuals with decompensated cirrhosis. Although several studies assessed different aspects of executive function, future studies of HCV-positive individuals would benefit from examining performance on measures of other executive functions, such as planning, decision-making, and response inhibition.

### Motor skills

Few studies have assessed *motor skills* (eg, finger tapping, fine motor coordination) in HCV infection. Three studies found impairments in this domain: Cordoba et al. [21], Vigil et al. [42], and Bieliauskas et al. [40]. Interestingly, although the first two studies used the same test (the Grooved Pegboard Test) to assess motor skill, Cordoba et al. [21] found motor deficits only in HCV-positive individuals with decompensated cirrhosis, whereas Vigil et al. [42] found impairments in relatively healthy HCV-positive individuals. Bieliauskas et al. [40] found that about 15% to 18% of HCV-positive individuals with advanced liver fibrosis have impaired motor skills.

### Visuoconstruction abilities

*Visuoconstruction abilities* involve the coordination of fine motor skills with spatial abilities [39]. These functions embrace two large classes of activities: drawing and building or assembly [39]. Most studies evaluating visuoconstruction skills in HCV have examined drawing; of the studies assessing these skills, only one reported visuoconstruction impairments in 9% of HCV-positive individuals [31]. Future studies assessing visuoconstruction abilities in HCV-positive individuals should include building and assembly tasks, which provide further information regarding visuoconstruction and motor abilities.

### Memory

Investigations of *memory* functioning in HCV typically focused on episodic memory, which refers specifically to memory for experienced events and includes information about the content of the event (eg, "what" was learned during the episode, including objects and word-lists) and the contextual details of the event (eg, "when" and "where" the episode occurred, including time, location, and source) [43]. Successful episodic memory involves three separable but strongly interrelated processes: encoding, consolidation, and retrieval. Encoding is the process by which new information is learned, and consolidation refers to the process of storing that information over time. Retrieval is the capacity to effectively access the stored information after a delay. Poor memory performance can result from a disruption of these processes individually or in combination; therefore, they are methodologically evaluated separately. Furthermore, examination of the profile of memory performance can provide information about the integrity of the underlying neural systems.

Measures of encoding typically represent the amount of information that an individual learns during one or more learning trials involving presentation of novel information. A total learning score, summed across multiple learning trials, is particularly informative for indicating how much new information has been acquired. Retrieval is a complex process that is measured in two ways: free recall and recognition. Free recall is a more demanding task that requires the individual to search the stored information and correctly access it on demand; retrieval failures may occur even when information was successfully learned and stored. On the other hand, recognition memory is an easier task in which previously learned information is presented alone (ie, yes/no recognition) or paired with a foil (ie, forced-choice recognition), and the individual indicates whether he or she recognizes it. Because consolidation is not measured directly, the relative ease of the recognition task inferentially provides a measure of how much of the learned information was stored over time. That is, poor recognition performance relative to learning suggests that learned information was forgotten over the delay; this outcome is typically observed when hippocampal structures are damaged. In contrast, poor recall performance relative to better recognition suggests a retrieval deficit, in which the individual has not forgotten the information but has difficulty accessing it without a cue; this pattern is associated with dysfunction in the frontostriatothalamocortical circuits that are thought to underlie successful retrieval.

Several studies that included measures of verbal learning and memory found HCV-associated impairments in these domains, suggesting that the impairments are rather robust among HCV-positive patients. For example, Hilsabeck et al. [20] found that 46% of HCV-positive patients with comorbidities were impaired on learning and 23% were impaired on recognition; 21% of HCV-positive patients without comorbidities were impaired on learning and 14% on recognition; and 15% of individuals with other liver disease were impaired on learning and 15% on recognition. When replicating these results on a different sample, investigators found that 16% of HCV-positive individuals with different comorbidities were impaired on learning and 14% had impaired recall [31].

In a recently published article, Huckans et al. [22•], found that 33% of HCV-positive individuals with a history of substance dependence were impaired on a test of verbal learning, whereas 44% were impaired on tests of visuospatial learning. Interestingly, among HCV-positive individuals with no history of substance dependence, 42% were deemed impaired on verbal learning and 46% on visuospatial learning. Karaivazoglou et al. [41•] also found that HCV-positive individuals performed worse than those who were seronegative on measures of verbal learning and recall; however, they found no differences in these measures between HCV-positive individuals and individuals infected with the hepatitis B virus. In contrast, Weissenborn et al. [9] found that HCV-positive individuals with moderate fatigue performed worse on learning than healthy controls, but those with mild fatigue performed similarly to controls. They found no differences in the recall domain.

## Learning and Memory Profiles in HCV Infection: A Data-based Examination

As reviewed above, significant evidence exists of HCV-associated episodic memory impairment in the literature;

**Table 2. Demographic characteristics of study participants**

| Variable | HCV+, *n* = 43 | HCV−, *n* = 49 |
|---|---|---|
| Age, mean (SD) | 45.3 (9.7) | 43.0 (9.7) |
| Education, mean (SD) | 12.4 (2.2) | 12.9 (2.3) |
| Ethnicity white, % *(n)* | 74% (32) | 67% (33) |
| Gender male, % *(n)* | 56% (24) | 61% (32) |
| Major depressive disorder, % *(n)* | | |
| Current | 3% (1) | 2% (1) |
| Lifetime | 38% (16) | 28% (14) |
| Substance dependence, % *(n)* | | |
| Alcohol | 46% (20) | 6% (3) |
| Cocaine | 49% (21) | 2% (1) |
| Marijuana | 27% (12) | 6% (3) |
| Stimulants | 35% (15) | 0% |
| Opioids | 32% (14) | 0% |
| Hallucinogens | 11% (4) | 0% |
| HCV characteristics, median (IQR) | | |
| HCV RNA serum, *IU/mL* | 5.9 (5.0, 6.2) | NA |
| Total bilirubin, *mg/dL* | 0.7 (0.4, 0.9) | NA |
| Albumin, *g/dL* | 0.4 (3.8, 4.2) | NA |
| AST-to-platelet ratio index | 0.4 (0.3, 0.9) | NA |

AST—aspartate transaminase; HCV—hepatitis C virus; IQR—interquartile range; NA—not applicable; SD—standard deviation.

however, no studies have examined the profile of memory deficits in an HCV-infected population. Delineation of a memory profile could enhance understanding of the effect of HCV on the brain, and may even have clinical utility in terms of informing detection and remediation of daily functioning difficulties. Accordingly, we present data on the profile of episodic memory functioning in a cohort of 43 HCV-positive individuals relative to a group of 49 demographically comparable, healthy participants (HCV-negative persons). We excluded individuals with a history of severe psychiatric illness, head trauma with loss of consciousness greater than 30 minutes, neurologic disease, or current substance abuse or dependence (ie, alcohol, cocaine, opioid, marijuana, stimulants, hallucinogens). Demographic and clinical characteristics of the study participants are presented in Table 2.

All participants were administered the Hopkins Verbal Learning Test–Revised (HVLT-R) and the Brief Visuospatial Memory Test–Revised (BVMT-R) as part of a larger neuropsychologic battery [44,45]. Briefly, the HVLT-R consists of three groups of four (nonconsecutive) semantically related words, which are read aloud at about 2-second interstimulus intervals. The HVLT-R includes three consecutive learning trials, a free-recall trial after a delay of 20 to 25 minutes, and a recognition trial (24 words consisting of 12 target words from the original list and 12 nontarget words). Six of the 12 nontarget words are semantically related to words on the original list. The BVMT-R consists of three consecutive learning trials involving presentation of a display comprising six geometric designs, a free-recall trial after a delay of 20 to 25 minutes, a recognition trial with 12 designs consisting of six target designs and six nontarget designs, and a copy trial to rule out visual deficits. The outcome variables for both tests were learning (the numbered of correctly recalled words/figures on trials 1 to 3), recall (the total correctly recalled words/figures on the free recall), and recognition (the number of correct recalled words/figures after being presented one more time). Raw scores for each test variable were converted into demographically adjusted T-scores.

Compared with seronegative participants, HCV-infected individuals had significantly lower T-scores on learning measures for the HVLT-R ($P$ = 0.04, Cohen's $d$ = -0.43) and the BVMT-R ($P$ = 0.04, $d$ = -0.44). Participants in both groups performed similarly on measures of delayed recall and recognition for both tests. Figure 1 displays the poorer learning performance in the HCV-positive group relative to healthy controls on the HVLT-R and BVMT-R, which is in contrast to the comparable delayed recall and recognition performance. Notably, a significant difference between the groups was also observed on the Retrieval Index of the HVLT-R ($P$ = 0.01, $d$ = -0.60), which is a measure of the discrepancy between delayed free recall and recognition performance.

These findings provide further evidence regarding the profile of learning and memory performance in HCV infection. The consistent finding of impaired learning across

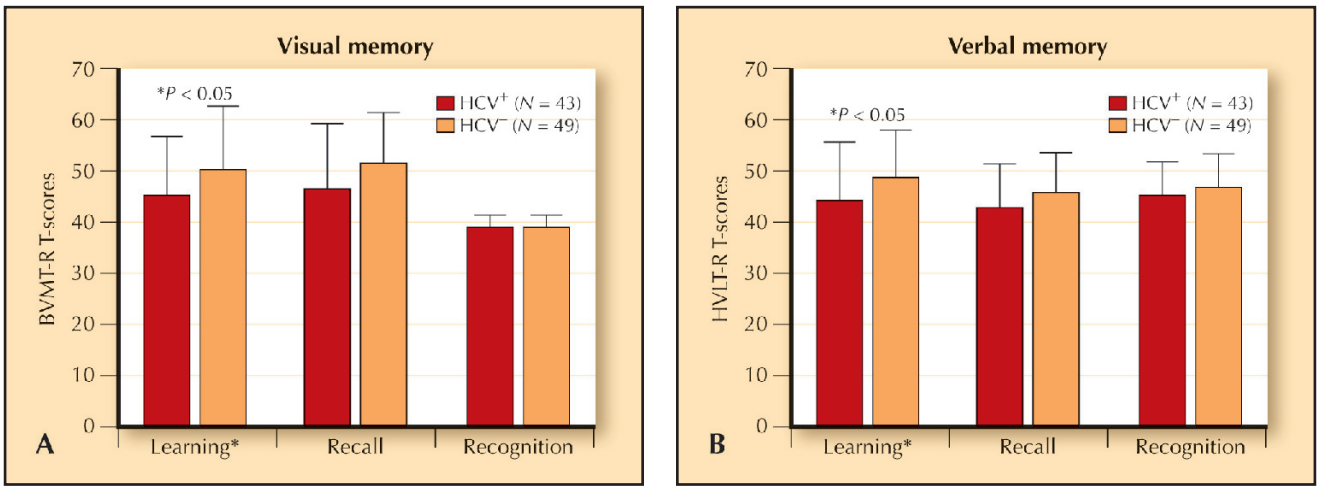


**Figure 1. A,** Brief Visuospatial Memory Test–Revised (BVMT-R) and **B,** Hopkins Verbal Learning Test–Revised (HVLT-R): learning, recall, and recognition measures in hepatitis C virus (HCV)–positive and HCV-negative groups (*$P < 0.05$).

verbal and visual modalities suggests that HCV-positive individuals have difficulty acquiring new information, which may be evidence of deficient encoding. Although findings in the literature regarding memory performance in HCV infection are mixed, our results suggest comparable performance of the HCV-positive participants relative to healthy individuals on delayed recall and recognition. However, the observed differences on the Retrieval Index of the HVLT-R revealed a greater discrepancy between delayed recall and recognition performance in the HCV-positive participants relative to the healthy participants, which may suggest that HCV-positive individuals had more difficulty freely recalling the information they had learned but were better able recognize that information when provided with a structure format. Although inferential, the poorer performance observed on measures of learning and the retrieval index in the HCV-positive group is consistent with deficient strategic encoding and retrieval processes that rely on frontostriatal systems [46], which are purportedly involved in HCV infection. The potential clinical implications of these findings include emphasizing the importance of recommendations for mnemonic compensatory strategies for HCV-positive patients, particularly regarding adherence to their medication regimen (eg, use of written instructions, calendars, alarms, pillboxes).

## Implications for Daily Living

In general, HCV-infected individuals have diminished health-related quality of life (HRQOL) compared with healthy adults [47]. With regard to the association between HRQOL and cognitive impairment among HCV-positive individuals, some studies found no associations between cognitive functioning and HRQOL [38], whereas other studies found small but significant correlations between these two factors. Specifically, poorer HRQOL is associated with worse performance on an electrophysiologic test of cognition [23], worse attention [21], and worse global neurocognitive performance [40].

In contrast to HRQOL, few studies have examined the independent performance of activities of daily living in this population. A study from our group found that, compared with HCV-negative individuals, HCV-positive individuals reported significantly greater declines in instrumental activities of daily living (IADL) (eg, managing finances, medication adherence, employment), and physical activities of daily living (PADL) (eg, bathing, laundry, home repairs) [42]. HCV-positive individuals with impaired psychomotor speed reported significantly greater IADL declines, whereas impaired fine-motor coordination was associated with declines in both IADLs and PADLs. Moreover, impaired psychomotor speed predicted IADL declines, whereas fine-motor coordination impairment predicted PADL declines. In general, HCV-positive persons have decreased HRQOL, and HCV-positive individuals with neuropsychologic impairment are at greater risk of poorer functional outcomes, including PADLs and IADLs.

In terms of medication adherence, several studies examined adherence to HCV treatment [48]. Using self-report, 69% to 98% of HCV-positive individuals reported being adherent to their medications, whereas 74% to 92% were adherent when measured by electronic devices [48]. HCV-positive individuals tend to be more adherent during the first 4 weeks of treatment and decrease adherence during the course of treatment. To our knowledge, no study has assessed the relationship between nonadherence and cognition in individuals with HCV infection.

## Conclusions

In summary, evidence from brain tissue, imaging, and neuropsychologic studies support the neurovirulence of HCV infection. Findings from the data presented here indicate that HCV-positive individuals have learning deficits although they have normal recall and recognition of

new information. HCV affects HRQOL and ADLs, and these impairments may be driven by cognitive dysfunction. Although several studies reported problems with medication adherence among HCV-positive persons, it is unknown whether cognitive impairment is related to nonadherence, as was shown in HIV infection [49,50]. Thus, future studies examining adherence to HCV treatment should assess the role of cognitive dysfunction in nonadherence. As with many conditions that cause subtle neurocognitive impairment, understanding the contributions of various cofactors (eg, substance dependence, neuropsychiatric symptoms) to neurocognitive impairment in HCV is critical. Also, future studies would benefit from additional assessments of everyday functioning (eg, financial management, driving) not only with self-report but also with laboratory measures, which have greater ecological validity. Importantly, knowledge is lacking regarding the vocational functioning of HCV-positive individuals and how neurocognitive impairments may moderate these abilities.

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## Disclosure

No potential conflicts of interest relevant to this article were reported.

## References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Laskus T, Radkowski M, Adair DM, et al.: **Emerging evidence of hepatitis C virus neuroinvasion.** *AIDS* 2005, **19(Suppl 3):**S140–S144.
2. Perry W, Hilsabeck RC, Hassanein TI: **Cognitive dysfunction in chronic hepatitis C: a review.** *Dig Dis Sci* 2008, **53:**307–321.
3. Forton DM, Taylor-Robinson SD, Thomas C: **Central nervous system changes in hepatitis C virus infection.** *Eur J Gastroenterol Hepatol* 2006, **18:**333–338.
4. Laskus T, Radkowski M, Wang LF, et al.: **Hepatitis C virus quasispecies in patients infected with HIV-1: correlation with extrahepatic viral replication.** *Virology* 1998, **248:**164–171.
5. Bolay H, Soylemezoglu F, Nurlu G, et al.: **PCR detected hepatitis C virus genome in the brain of a case with progressive encephalomyelitis with rigidity.** *Clin Neurol Neurosurg* 1996, **98:**305–308.
6. Forton DM, Allsop JM, Main J, et al.: **Evidence for a cerebral effect of the hepatitis C virus.** *Lancet* 2001, **358:**38–39.
7. Letendre S, Paulino AD, Rockenstein E, et al.: **Pathogenesis of hepatitis C virus coinfection in the brains of patients infected with HIV.** *J Infect Dis* 2007, **196:**361–370.
8. Wilkinson J, Radkowski M, Laskus T: **Hepatitis C virus neuroinvasion: identification of infected cells.** *J Virol* 2009, **83:**1312–1319.
9. Weissenborn K, Krausse J, Bokemeyer M, et al.: **Hepatitis C virus infection affects the brain—evidence from psychometric studies and magnetic resonance spectroscopy.** *J Hepatol* 2004, **41:**845–851.
10. Taylor MJ, Letendre SL, Schweinsburg BC, et al.: **Hepatitis C virus infection is associated with reduced white matter N-acetylaspartate in abstinent methamphetamine users.** *J Int Neuropsychol Soc* 2004, **10:**110–113.
11. Forton DM, Thomas HC, Murphy CA, et al.: **Hepatitis C and cognitive impairment in a cohort of patients with mild liver disease.** *Hepatology* 2002, **35:**433–439.
12. McAndrews MP, Farcnik K, Carlen P, et al.: **Prevalence and significance of neurocognitive dysfunction in hepatitis C in the absence of correlated risk factors.** *Hepatology* 2005, **41:**801–808.
13. Forton DM, Hamilton G, Allsop JM, et al.: **Cerebral immune activation in chronic hepatitis C infection: a magnetic resonance spectroscopy study.** *J Hepatol* 2008, **49:**316–322.
14. Weissenborn K, Krause J, Bokemeyer M, et al.: **Monoaminergic neurotransmission is altered in hepatitis C virus infected patients with chronic fatigue and cognitive impairment.** *Gut* 2006, **55:**1624–1630.
15. Weissenborn K, Tryc AB, Heeren M, et al.: **Hepatitis C virus infection and the brain.** *Metab Brain Dis* 2009, **24:**197–210.
16. Burggren AC, Zeineh MM, Ekstrom AD, et al.: **Reduced cortical thickness in hippocampal subregions among cognitively normal apolipoprotein E e4 carriers.** *Neuroimage* 2008, **41:**1177–1183.
17. Ernst T, Chang L, Arnold S: **Increased glial metabolites predict increased working memory network activation in HIV brain injury.** *Neuroimage* 2003, **19:**1686–1693.
18. Fontana RJ, Bieliauskas LA, Back-Madruga C, et al.: **Cognitive function in hepatitis C patients with advanced fibrosis enrolled in the HALT-C trial.** *J Hepatol* 2005, **43:**614–622.
19. Weissenborn K, Ennen JC, Schomerus H, et al.: **Neuropsychological characterization of hepatic encephalopathy.** *J Hepatol* 2001, **34:**768–773.
20. Hilsabeck RC, Perry W, Hassanein TI: **Neuropsychological impairment in patients with chronic hepatitis C.** *Hepatology* 2002, **35:**440–446.
21. Cordoba J, Flavia M, Jacas C, et al.: **Quality of life and cognitive function in hepatitis C at different stages of liver disease.** *J Hepatol* 2003, **39:**231–238.
22.• Huckans M, Seelye A, Parcel T, et al.: **The cognitive effects of hepatitis C in the presence and absence of a history of substance use disorder.** *J Int Neuropsychol Soc* 2009, **15:**69–82.
This article describes one of the few studies directly assessing the effects of both HCV virus and substance abuse.
23. Kramer l, Bauer E, Funk G, et al.: **Subclinical impairment of brain function in chronic hepatitis C infection.** *J Hepatol* 2002, **37:**349–354.
24. Ryan EL, Morgello S, Isaacs K, et al.: **Neuropsychiatric impact of hepatitis C on advanced HIV.** *Neurology* 2004, **62:**957–962.
25. von Giesen HJ, Heintges T, Abbasi-Boroudjeni N, et al.: **Psychomotor slowing in hepatitis C and HIV infection.** *J Acquir Immune Defic Syndr* 2004, **35:**131–137.
26. Letendre SL, Cherner M, Ellis RJ, et al.: **Individuals co-infected with hepatitis C (HCV) and HIV are more cognitively impaired than those infected with either virus alone [abstract].** *J Neurovirol* 2002, **8:**27–28.
27. Hinkin CH, Castellon SA, Levine AJ, et al.: **Neurocognition in individuals co-infected with HIV and hepatitis C.** *J Addict Dis* 2008, **27:**11–17.
28. Wessely S, Pariante C: **Fatigue, depression and chronic hepatitis C infection.** *Psychol Med* 2002, **32:**1–10.
29. Obhrai J, Hall Y, Anand BS: **Assessment of fatigue and psychologic disturbances in patients with hepatitis C virus infection.** *J Clin Gastroenterol* 2001, **32:**413–417.

30. Fontana RJ, Hussain KB, Schwartz SM, et al.: **Emotional distress in chronic hepatitis C patients not receiving antiviral therapy.** *J Hepatol* 2002, **36:**401–407.
31. Hilsabeck RC, Hassanein TI, Carlson MD, et al.: **Cognitive functioning and psychiatric symptomatology in patients with chronic hepatitis C.** *J Int Neuropsychol Soc* 2003, **9:**847–854.
32. Kramer L, Bauer E, Funk G, et al.: **Subclinical impairment of brain function in chronic hepatitis C infection.** *J Hepatol* 2002, **37:**349–354.
33. Vial T, Descotes J: **Clinical toxicity of the interferons.** *Drug Saf* 1994, **10:**115–150.
34. van Gorp WG, Satz P, Hinkin C, et al.: **Metacognition in HIV-1 seropositive asymptomatic individuals: self-ratings versus objective neuropsychological performance. Multicenter AIDS Cohort Study (MACS).** *J Clin Exp Neuropsychol* 1991, **13:**812–819.
35. Lieb K, Engelbrecht MA, Gut O, et al.: **Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFN alpha): results from a prospective study.** *Eur Psychiatry* 2006, **21:**204–210.
36. Pawelczyk T, Pawelczyk A, Strzelecki D, et al.: **Pegylated interferon alpha and ribavirin therapy may induce working memory disturbances in chronic hepatitis C patients.** *Gen Hosp Psychiatry* 2008, **30:**501–508.
37.• Fontana RJ, Bieliauskas LA, Lindsay KL, et al.: **Cognitive function does not worsen during pegylated interferon and ribavirin retreatment of chronic hepatitis C.** *Hepatology* 2007, **45:**1154–1163.
This article describes the most comprehensive study assessing the effects on cognition of HCV treatment.
38. Thein H, Maruff P, Krahn M, et al.: **Improved cognitive function as a consequence of hepatitis C virus treatment.** *HIV Med* 2007, **8:**520–528.
39. Lezak MD: *Neuropsychological Assessment,* edn 4. New York: Oxford University Press; 2004.
40. Bieliauskas LA, Back-Madruga C, Lindsay KL, et al.: **Clinical relevance of cognitive scores in hepatitis C patients with advanced fibrosis.** *J Clin Exp Neuropsychol* 2006, **28:**1346–1361.
41.• Karaivazoglou K, Assimakopoulos K, Thomopoulos K, et al.: **Neuropsychological function in Greek patients with chronic hepatitis C.** *Liver Int* 2007, **27:**798–805.
This article describes one of the few studies comparing HCV-positive individuals with HBV-positive individuals.
42. Vigil O, Posada C, Woods SP, et al.: **Impairments in fine-motor coordination and speed of information processing predict declines in everyday functioning in hepatitis C infection.** *J Clin Exp Neuropsychol* 2008:1–11.
43. Tulving E: **Episodic and semantic memory.** In *Organization of Memory.* Edited by Tulving E, Donaldson W. Oxford, England: Academic Press; 1972.
44. Benedict RH, Schretlen D, Groninger L, Brandt J: **Hopkins Verbal Learning Test-Revised: normative data and analysis of inter-form and test-retest reliability.** *Clin Neuropsychol* 1998, **12:**43–55.
45. Benedict RH: *Brief Visuospatial Memory Test-Revised.* Odessa, FL: Psychological Assessment Resources; 1997.
46. Moscovitch M: **Cognitive resources and dual-task interference effects at retrieval in normal people: the role of the frontal lobes and medial temporal cortex.** *Neuropsychology* 1994:524–534.
47. Spiegel BM, Younossi ZM, Hays RD, et al.: **Impact of hepatitis C on health related quality of life: a systematic review and quantitative assessment.** *Hepatology* 2005, **41:**790–800.
48. Weiss JJ, Bräu N, Stivala A, et al.: **Review article: adherence to medication for chronic hepatitis C—building on the model of human immunodeficiency virus antiretroviral adherence research.** *Aliment Pharmacol Ther* 2009, **30:**14–27.
49. Hinkin CH, Castellon SA, Durvasula RS, et al.: **Medication adherence among HIV+ adults: effects of cognitive dysfunction and regimen complexity.** *Neurology* 2002, **59:**1944–1950.
50. Woods SP, Dawson MS, Weber E, et al.: **Timing is everything: antiretroviral nonadherence is associated with impairment in time-based prospective memory.** *J Int Neuropsychol Soc* 2009, **15:**42–52.