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REVIEW ARTICLE

Cognitive Dysfunction in Chronic Hepatitis C: A Review

William Perry · Robin C. Hilsabeck · Tarek I. Hassanein

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Abstract The hepatitis C virus (HCV) is a common blood-borne illness that affects up to 2% of the world's population and almost 4 million Americans. Cognitive impairment, or difficulty with thinking, has become a well-established symptom in persons with end stage liver disease. It was previously assumed that cognitive impairment was a consequence of cirrhosis-associated hepatic encephalopathy. Recent evidence, however, suggests that approximately one-third of people with chronic HCV experience cognitive impairment even in the absence of cirrhosis and that its occurrence is unrelated to other indices of liver function, such as laboratory values, viral load, and genotype. In the present review, evidence outlining the presence of cognitive deficits associated with HCV, possible etiological factors, effects of antiviral therapy, and co-infection with human immunodeficiency virus (HIV) is presented. Implications of these findings and directions for future work are discussed.

Keywords Chronic hepatitis C · Cognitive dysfunction · Neuropsychological impairment · Chronic liver disease · Neuroimaging · Co-infection

The hepatitis C virus (HCV) represents the second most common blood-borne illness in the world, affecting up to 2% of the world's population and almost 4 million Americans [1, 2]. Moreover, the number of infected people with chronic HCV complications is expected to triple over the next decade [3]. Chronic HCV infection is, in fact, a leading cause of cirrhosis and liver cancer [4]. Cognitive impairment, or difficulty with thinking, has been well documented in persons with chronic liver disease and, until recently, was assumed to be a consequence of cirrhosis-associated hepatic encephalopathy (HE). Conditions such as portal-systemic shunting can result in cerebral dysfunction hallmarked by decreased recent memory, fluctuating consciousness, and disorientation thought to be an outcome of high ammonia concentration and astrocyte swelling [5, 6]. However, there is growing evidence that there are fundamental cognitive deficits in many patients with HCV prior to the development of cirrhosis that are unrelated to indices of liver dysfunction, viral load, or genotype [7–16]. In the following review, we outline the current evidence that supports the presence of cognitive deficits associated with HCV, possible etiological factors, effects of antiviral therapy, and co-infection with human immunodeficiency virus (HIV). We conclude with a discussion of the implications of these findings and directions for future work.

Cognitive dysfunction in HCV patients without cirrhosis

Early in the disease process, patients with HCV report symptoms that include fatigue, malaise, weakness, anorexia and, occasionally, jaundice. Also prominent among patients with HCV are complaints of problems with thinking that have been described as "brain fog" or problems with attending to and recalling everyday information [7, 8]. Cognitive difficulties such as these can interfere with

W. Perry · R. C. Hilsabeck
Department of Psychiatry, Hepatology Neurobehavioral Research Program, UCSD Liver Center, University of California, 200 West Arbor Drive, San Diego, CA 92108-8707, USA

T. I. Hassanein (✉)
Department of Medicine, Hepatology Neurobehavioral Research Program, UCSD Liver Center, University of California, 200 West Arbor Drive, San Diego, CA 92108-8707, USA
e-mail: thassanein@ucsd.edu

the completion of activities of daily living and with the ability to maintain independent functioning. While assessing mental status using clinical observation may be useful when evaluating patients with overt HE, patients with subtle forms of cognitive deficits require a more sensitive, objective assessment using well-established neuropsychological or psychophysiological instruments [17].

Concurrent with the epidemic of HCV came increasing numbers of patients without cirrhosis complaining of subtle cognitive impairment hallmarked by difficulty in concentrating and slowed thinking. Hilsabeck and colleagues [11] examined cognitive functioning in patients with HCV from a tertiary care liver clinic over a 10-month period; more specifically, they investigated the relationship among parameters of disease severity and performance on neuropsychological tests. Sixty-six patients with chronic HCV and 14 patients with other chronic liver diseases were administered a brief battery of neuropsychological tests assessing attention, visuoconstructional ability, learning, memory, and psychomotor speed. Impaired performance was determined using the established criterion of one standard deviation below the published normative demographic-corrected mean for each measure. Cognitive impairment in patients with HCV ranged from 0% on a visuoconstructional task to 82% on a measure of sustained attention. There was a trend for patients with HCV to perform more poorly than patients with other chronic liver diseases, and HCV patients with comorbid chronic medical conditions performed the worst of all. In addition, there was a significant relationship between neuropsychological test performance and fibrosis stage, with a poorer test performance associated with greater fibrosis. However, HCV patients with minor hepatic injury as well as those with cirrhosis exhibited cognitive dysfunction, particularly attention and concentration difficulties, and the pattern of impairment suggested involvement of frontal-subcortical pathways.

Other studies in which objective neuropsychological tests were conducted demonstrated that HCV patients without cirrhosis had significant deficits on measures of attentional processing [8, 13]. In a follow-up study, Hilsabeck and others [12] confirmed the pattern and percentage of impairment on the neuropsychological tests in a separate sample of HCV patients. They found that none of the HCV patients exhibited impaired constructional abilities, and few patients demonstrated non-verbal recall deficits. In contrast, up to 50% of HCV patients were impaired on tests of concentration, working memory (the ability to hold and manipulate information in short-term storage), sustained attention, and processing speed, with the greatest prevalence of impairment on tests of sustained attention and visuomotor processing speed (i.e., 38–49%). This pattern of cognitive deficits exhibited by HCV patients is most consistent with frontal-subcortical dysfunction and is similar to that reported in patients with HIV.

An independent group of researchers recently replicated these findings in a large sample of patients ($N = 201$) entering a clinical trial for non-responders to interferon therapy [16]. These authors reported that 33% of their sample was impaired on at least one-third of their comprehensive neuropsychological test battery, and the pattern of findings was consistent with subcortical cognitive inefficiency. Thus, there is a mounting body of evidence that approximately one-third of HCV patients have a pattern of deficits involving subcortical neurocircuitry similar to that found among patients with HIV.

Cognitive deficits suggestive of frontal-subcortical dysfunction in HCV patients have also been supported using other assessment methods. Forton and colleagues [7, 8], for example, found cerebral metabolic abnormalities in the frontal white matter and basal ganglia of HCV patients using proton magnetic resonance spectroscopy (^{1}H MRS), and similar findings have been reported by other researchers [13–15]. In addition, cognitive dysfunction in HCV patients with little or no fibrosis has been detected using electroencephalogram (EEG) and P300 event-related potentials [9, 10, 13]. As noted by others [10, 15, 18], neurophysiologic and neuroimaging measures are important assessment methods for characterizing cognitive dysfunction in HCV as they may be able to detect dysfunction prior to its behavioral manifestation, they can shed insight into neuropathophysiology, and they are not subject to biases inherent in tests batteries or self-report measures, such as language proficiency, socio-cultural differences, level of education, and psychological insight.

For these reasons, our group also has begun to study HCV patients using a psychophysiological measure of attentional processing called prepulse inhibition (PPI). PPI occurs when a weak pre-stimulus presented 30–500 ms prior to a startling stimulus results in a reduction in the magnitude of the blink reflex as measured by electromyography. Intact PPI is thought to reflect the brain's ability to filter irrelevant sensory stimuli so that the organism can direct attention and cognitive effort to relevant and important information [19]. PPI is an automatic, involuntary phenomenon [20] and, therefore, not heavily influenced by extraneous factors such as fatigue, effort, intellectual functioning, level of education, among others.

In a small pilot study using our standard PPI paradigm [21–23], HCV patients demonstrated lower PPI in both the 60 and 120 ms conditions compared to an archival group of healthy control participants. These results support the proposal that PPI is a useful and sensitive measure of attentional processing deficits in HCV patients; they are also particularly intriguing as PPI appears to be regulated

by a forebrain cortico-striatial-pallidal-thalamic circuit (CSPT) [24]. Other patient populations with known dysfunction in the CSPT circuit, such as Parkinson's disease [25] and Huntington's disease [26], also demonstrate impaired PPI. Thus, the present results, in combination with findings from neuropsychological tests, MRS, EEG, and P300, provide strong support for the presence of an attentional deficit mediated by frontal-subcortical circuitry in a group of patients infected with HCV. A summary of studies examining cognitive dysfunction in non-cirrhotic patients with HCV can be found in Table 1.

Etiology of cognitive dysfunction in HCV

While most studies have documented cognitive dysfunction in HCV patients, none have provided strong support for any particular etiology. Factors hypothesized to account for cognitive dysfunction in HCV include premorbid characteristics and lifestyle choices, comorbid psychiatric disease, a direct effect of the virus on the brain, and/or secondary effects of the inflammatory process [27, 28]. The evidence for each possible etiology is reviewed below.

Premorbid characteristics and lifestyle choices

The possibility that cognitive dysfunction in HCV may be explained by premorbid personality characteristics and lifestyle factors, such as substance use, has been suggested given the large body of literature documenting cognitive deficits in persons who abuse substances [29, 30]. Intravenous drug use (IVDU) is the primary risk factor for chronic HCV infection, with approximately 60–70% of persons with chronic HCV indicating a history of IVDU [31]. Up to 98% of IVDUs have been found to have chronic HCV, although this number varies widely, usually between 30 and 70% [32]. Individuals with alcohol dependence also have higher rates of chronic HCV infection than the general population (i.e., 5 vs. 2%), and almost 50% of persons with alcoholic liver disease also have chronic HCV infection [33]. Studies using structured clinical interviews to diagnose substance use disorders among HCV patients in tertiary liver clinics indicate that 27–56% of these individuals meet diagnostic criteria for past alcohol abuse/dependence, and 44–46% meet criteria for history of other substance abuse/dependence [34, 35]. In veteran populations with HCV, the prevalence of substance use disorders is also high, with reports of 78–86% for alcohol, 39–69% for cocaine, 24–43% for marijuana, and 60–69% for polysubstance abuse/dependence [36, 37].

The effect of premorbid factors on cognitive functioning in chronic HCV patients was addressed by Forton and colleagues [8]. These researchers studied 27 HCV-infected individuals and 16 persons who had been exposed to HCV but were HCV RNA negative on at least two occasions 6 months apart. A comparison group of HCV-cleared individuals was chosen specifically to control for lifestyle and personality factors that may be associated with HCV acquisition, and approximately half of the participants in each group reported a history of IVDU. Participants were administered a computerized battery of neuropsychological tests and self-report measures of depression, anxiety, fatigue, and quality of life. The results showed that the HCV-infected group was impaired on more neuropsychological tests than the HCV-cleared group but that there were no significant differences between individuals with and without IVDU histories regardless of HCV status. The authors concluded that people with HCV infection have cognitive deficits that are not accounted for by a history of substance use (note, however, that none of their participants indicated regular excessive alcohol consumption). Kramer and colleagues [9] also failed to find significantly greater cognitive dysfunction in a subgroup of 23 patients with a history of IVDU or between patients with and without histories of alcohol consumption or with minimal/occasional alcohol use compared to moderate/substantial alcohol use. Subsequent studies have shown that mild cognitive dysfunction is still apparent in HCV patients when you exclude persons with histories of IVDU, substance abuse disorder, or drug dependence within the past 7 years [13, 15].

Psychiatric disease

In addition to the physical problems associated with chronic HCV, there is a high rate of psychiatric comorbidity, with up to 40% of HCV-infected persons meeting diagnostic criteria for a concurrent, active psychiatric disorder [34–37]. Depression is the most common comorbid psychiatric disorder, with a prevalence ranging from 28 to 50%, but the prevalence of anxiety disorders also range from 18 to 41% [34–37]. The prevalence of comorbid HCV and psychiatric disorders have been studied in veteran samples, revealing rates of 9–16% for bipolar disorder, 17–24% for psychotic disorders, and 30% for personality disorders, with antisocial disorder most common at 16% [36, 37].

High levels of general psychological distress and self-reported mood disturbance are also apparent in persons with chronic HCV [38–40]. Fatigue is the most frequent symptom reported [41], with depressive and anxiety symptomatology also highly reported [39]. Using reliable self-report measures, such as the Beck Depression and Anxiety Inventories [42, 43] and the Brief Symptom Inventory [44], approximately 25–40% of HCV patients report clinically significant symptomatology [39, 45].

Table 1 Studies of cognitive dysfunction in non-cirrhotic patients with hepatitis C virus

Study	Sample	Sample characteristics	Measures	Findings
Forton et al. [7]	30 HCV 29 controls 12 HBV 0% cirrhotic	IVDU = 67% ETOH = NA	^{1}H MRS	Increased CHO in HCV group; Not related to IVDU
Forton et al. [8]	27 HCV 16 HCV cleared 29 controls (historic for ^{1}H MRS) 0% cirrhotic	IVDU = 48% HCV; 50% HCV cleared ETOH = 0%	(1) Computerized cognitive battery assessing attention, working memory, and episodic secondary memory (2) Self-report measures of depression, anxiety, and fatigue (3) ^{1}H MRS (N = 17 HCV)	HCV subjects impaired on more tasks than HCV cleared; Concentration and speeded processing most impaired; Increased CHO in HCV group; No relationship to IVDU, depression, QOL, fatigue, and serum ALT
Kramer et al. [9]	100 HCV 100 Controls 25% cirrhotic	IVDU = 23% ETOH = 3%	(1) P300 evoked potentials (2) Self-report measures of QOL and fatigue	16% HCV abnormal P300 latencies; No relationship to fibrosis, viral load, IVDU, or fatigue; Weak association to QOL
Kramer et al. [10]	120 HCV 100 Controls 21% cirrhotic	IVDU = 27%	(1) P300 evoked potentials (2) Self-report measures of QOL and fatigue	18% HCV abnormal P300, with peak latencies delayed and amplitudes reduced; Fatigue and age related to QOL but not P300 abnormalities
Hilsabeck et al. [11]	44 HCV 22 HCV + Comorbid medical conditions 14 other liver disease 50% cirrhotic	Drugs = 67% ETOH = 15%	Cognitive tests of visuoconstruction, learning, retention, attention, psychomotor speed, and mental flexibility	Deficits in attention, learning, psychomotor speed, and mental flexibility; Worst in HCV + comorbid medical conditions; Greater fibrosis related to greater impairment
Hilsabeck et al. [12]	21 HCV 33% cirrhotic	IVDU = 71% ETOH = 19%	(1) Cognitive tests of visuoconstruction, learning, retention, attention, psychomotor speed, and mental flexibility (2) Self-report measures of depression, anxiety, fatigue, and cognitive complaints	Deficits in up to 38% with complex attention and working memory most affected; Greater fibrosis related to greater impairment; No relationship to depression, anxiety, fatigue, or cognitive complaints
Cordoba et al. [5]	120 HCV 40 Controls 66% cirrhotic	IVDU = 3% ETOH = 0%	(1) Cognitive tests of visuoperception, verbal fluency, learning, retention, attention, processing and psychomotor speed, mental flexibility, and manual dexterity (2) Self-report measures of QOL, depression, and anxiety	Cognitive dysfunction not related to reduced QOL; Cognitive impairment greatest in decompensated cirrhotics
Weissenborn et al. [13])	15 HCV with mild fatigue 15 HCV with moderate fatigue 15 Controls 0% cirrhotic	Excluded	(1) Cognitive tests of visuoperception, construction, learning, retention, attention, and psychomotor speed (2) Self-report measures of depression and anxiety (3) EEG (4) ^{1}H MRS	Deficits in attention, EEG slowing, and decreased NAA in both HCV groups; Depression and anxiety higher in HCV groups but cannot account for cognitive dysfunction

Table 1 continued

Study	Sample	Sample characteristics	Measures	Findings
Taylor et al. [14]	6 HCV/METH	IVDU = 83% HCV/METH; 50% METH	(1) ^{1}H MRS	Decreased NAA in frontal white matter in HCV/METH group; Decreased NAA in frontal gray matter in both METH groups; 83% HCV/METH and 50% METH rated globally impaired on test battery
	10 METH	ETOH and Drugs other than METH excluded	(2) Comprehensive cognitive test battery (specific tests or domains not reported)	
	10 Controls			
	% Cirrhotic – NAA			
McAndrews et al. [15]	37 HCV	Excluded	(1) Cognitive tests of learning, retention, attention, processing speed, and cognitive flexibility	Deficits in learning; Increased CHO and decreased NAA in central white matter; No relationship to fibrosis, depression, or fatigue
	42 Controls		(2) ^{1}H MRS	
	0% cirrhotic		(3) Self-report measures of depression and fatigue	
Fontana et al. [16]	201 HCV	IVDU = 46%	(1) Cognitive tests of verbal fluency, learning, retention, processing speed, and cognitive flexibility	33% cognitively impaired; Deficits in learning, complex working memory, and reaction time; Not related to fibrosis, substance use, lifetime psychiatric disorder, or mood disturbance
	38% cirrhotic	ETOH = 50%	(2) Self-report measures of depression and global emotional distress	

HCV, Hepatitis C; HBV, hepatitis B; IVDU, intravenous drug use; ETOH , alcohol; ^{1}H MRS, proton magnetic resonance spectroscopy; CHO, choline; QOL, quality of life; ALT, alanine aminotransferace; EEG, electroencephalogram; METH, methamphetamine; NAA, N-acetylaspartate

The presence of comorbid psychiatric symptomatology has been postulated as an etiological factor in the cognitive dysfunction exhibited by persons with chronic HCV as depression and anxiety have been shown to independently impact cognitive functioning, particularly on measures of attention, concentration, and processing speed [46]. To address this, our group examined the relationship between self-reported symptoms of cognitive dysfunction and psychiatric symptomatology (i.e., depression, anxiety, and fatigue) and neuropsychological test performance [12]. We found no performance differences between HCV-infected patients reporting high and low levels of cognitive dysfunction and psychiatric symptoms, respectively. These findings have been confirmed by other groups [10] and supported by subsequent studies that have documented cognitive deficits in people with chronic HCV and no comorbid psychiatric conditions [13, 15, 16].

A few studies have reported significant relationships between cognitive test performance and self-reported symptomatology, particularly depression and fatigue [8, 13]. However, these findings have been variable and of questionable clinical significance. For example, Forton and colleagues [8] showed that while an HCV-infected group endorsed greater depressive symptoms than an HCV-cleared group, most associations between neuropsychological measures and depressive symptoms were not significant. The only exception was a moderate correlation between the Beck Depression Inventory and a measure of sustained attention ($r = -0.43$), suggesting that as depressive symptoms increase, the ability to sustain attention decreases. It is important to note, however, that the median depression score in both groups was well below the suggested cutoff for clinically significant symptomatology. Thus, while it is possible that the depressive symptoms found among HCV patients may contribute to their cognitive problems, it appears unlikely that the presence of psychiatric symptoms alone can account for the cognitive deficits associated with HCV. A more parsimonious scenario is that cognitive dysfunction and mild psychiatric symptoms are part of the same neuropsychiatric syndrome experienced by patients with chronic HCV.

Direct effects of the virus

It has been proposed that cognitive dysfunction associated with HCV is due to the virus itself infecting the brain [47–49]. This hypothesis is based on data showing that HCV replicates in peripheral blood mononuclear cells (PBMCs) and bone marrow [50–53], which serve as precursors for microglial cells and perivascular macrophages within the brain [54]. Thus, HCV may be introduced into the central nervous system via a "Trojan horse" mechanism such as that hypothesized to occur in patients with HIV [55]. The "Trojan horse" hypothesis proposes that infected monocytes migrate to the brain and replace microglial cells, which are located predominantly in the cerebral white matter. In vitro studies have confirmed that HCV can replicate in human macrophages [56, 57].

Any effect of the virus itself on cognitive functioning is likely to be small, however, based on data showing that the replication of HCV quasi-species is very low and sometimes undetectable in the brain [58, 59] and the lack of studies demonstrating a relationship between viral load in serum and cognitive dysfunction [11–13, 15, 16]. Moreover, HCV RNA is not always detectable in the cerebrospinal fluid (CSF) of HCV patients although it is evident in serum [60, 61], and when detectable, CSF viral loads have been found to be much lower than those in serum [62].

Secondary effects of the inflammatory process

Chronic activation of the immune system also may account for cognitive dysfunction exhibited by patients with chronic HCV, as there is increasing appreciation of a possible role of cytokines mediating cognition [63–65]. It is well known that cytokines are regulated in cascades and involve positive and negative feedback loops within the brain. Once an individual is infected with HCV, cytokines such as interleukin (IL)-2, IL-4, IL-10, and interferon-gamma are produced [66] and may continue to be elevated for as many as 20–30 years and longer. During this time of chronic infection, certain cytokines like interferon-alpha (IFN-α) and tumor necrosis factor-alpha (TNF-α), may cross the blood-brain barrier (BBB), especially at the site of the organum vasculosum laminae terminalis, to affect brain functioning [67–69]. It also may be the case that even small amounts of HCV in the brain induce a local inflammatory response, as Radkowski and colleagues [70] have demonstrated that macrophages infected with HCV in vitro can induce TNF-α and IL-8.

Cytokines are postulated to affect brain functioning indirectly by transmitting signals via the vagus nerve or other visceral afferent neuronal pathways and by binding to the cerebral vascular endothelium and inducing secondary messengers such as prostaglandins and nitric oxide [71, 72]. Moreover, cytokines have been shown to have neuromodulatory effects on the CNS through stimulation of neuroendocrine pathways and various neurotransmitter systems [63, 73]. Another possible contributor to cognitive dysfunction associated with chronic immune activation is microglial cells infected via the Trojan horse mechanism described above. Microglia are known to release excitatory amino acids that can induce neuronal cell death via excitotoxicity, and they can exert a neuromodulary role

through the release of neurotoxins and other neurochemicals [74].

Effects of antiviral therapy on cognitive functioning in patients with HCV

A prime example of a cytokine affecting cognitive functioning can be found in the literature examining the administration of exogenous IFN-α, the primary antiviral therapy for HCV. Exogenous IFN-α has been shown to adversely affect cognitive functioning in both healthy volunteers [75] and clinical populations [76–79]. At present, information about the effects of IFN-α on cognitive functioning in HCV patients is limited but suggests a negative impact. For example, Kamei and colleagues [80, 81] found diffuse slowing on quantitative EEG and reduced performances on a cognitive screening measure after 2 and 4 weeks of IFN-α therapy which reversed after the end of treatment. Using positron emission tomography (PET) and a short battery of neuropsychological tests, Juengling and colleagues [82] found hypometabolism in the bilateral prefrontal and right parietal cortex, hypermetabolism in the bilateral putamen (left greater than right), right thalamus, and left occipital cortex, and reduced verbal learning after 3 months of IFN-α therapy.

We examined the effects of IFN-α therapy using brief neuropsychological tests and compared the results to a group of untreated HCV patients [83]. All participants were tested at baseline and approximately 6–9 months later. The IFN-α group was tested about 1 month prior to initiating treatment. Results revealed that there were no significant differences on simple attentional measures, but the treated group performed significantly worse than the untreated patients on a measure of complex attention and working memory. We interpreted these findings as support that frontal-subcortical systems are adversely affected by IFN-α in HCV patients and that the prefrontal lobe functions of working memory may be the most vulnerable. Four additional studies have reported similar results and conclusions [84–87]. Moreover, these subsequent studies have found no relationship between cognitive dysfunction and self-reported depressive and anxious symptomatology. Further, Reichenberg and colleagues [88] reported no association between depression during IFN-α therapy and subjective cognitive complaints. Interestingly, 16% of their HCV patients continued to complain of cognitive problems after completion of the treatment. Clearly, additional research is needed to further understand the extent of IFN-α's impact on cognition. Functional neuroimaging may be particularly helpful in this regard as it allows exploration of key regions of interest, such as the anterior cingulate cortex and prefrontal cortex [89]. Findings from the above studies are summarized in Table 2.

Cognitive dysfunction in HCV patients co-infected with HIV

It is well known that HCV patients are often co-infected with other viruses such as HIV. It has been reported that 30% of HIV patients are infected with HCV [91], and rates of HCV/HIV co-infection in IVDUs are alarmingly high at 60–90% [92]. Given that cognitive dysfunction also is exhibited by persons with HIV infection [93], researchers have begun to examine how the presence of both infections impacts cognitive functioning.

We, as well as several other groups, are studying neuropsychological performance in individuals co-infected with HCV/HIV. We studied two groups of relatively healthy HCV-infected and HCV/HIV co-infected patients [94]. We tested 47 HCV-alone and 29 HCV/HIV co-infected patients on tests of attention and psychomotor speed, and their performance was compared to normative samples. Our results were consistent with previous reports that HCV patients– independent of co-infection status – demonstrate deficits on neuropsychological measures of attention, concentration and psychomotor speed, and liver disease severity was associated with poorer test performance. However, there were no significant differences between patients with HCV-alone and HCV/HIV co-infected patients on neuropsychological measures. Other studies have failed to find significant differences between co-infected and mono-infected persons on individual neuropsychological measures, although trends for greater impairment in co-infected persons were suggested [95, 96]. Martin and colleagues [97] demonstrated a differential pattern of impairment on a cognitive task of reaction time and response inhibition, with HCV-infected patients exhibiting overall slowed processing speed and HIV-infected patients showing impaired executive ability (Table 3).

Data suggesting an additive effect of co-infection on cognitive dysfunction is accumulating, especially when general cognitive functioning is the criterion rather than individual test performance [97–101]. In one of the largest studies to date, Letendre and colleagues [101] assessed the effects of HCV, HIV, and methamphetamine (METH) on neuropsychological functioning among 526 subjects. They studied four groups: an HIV-negative/METH-negative group, an HIV-negative/METH-positive group, an HIV-positive/METH-negative group, and an HIV-positive/METH-positive group. Among the 526 subjects, 112 were also HCV-positive. All subjects underwent an extensive neuropsychological battery, assessing seven cognitive domains. The authors found that HCV-positive subjects performed worse than HCV-negative subjects on the neuropsychological testing. This finding was present even after controlling for HIV, METH status, Centers for Disease Control stage, and antiviral use. The authors inter-

Table 2 Studies of cognitive dysfunction associated with IFN-α therapy in patients with HCV

Study	Sample	IFN dose	Measures	Assessment intervals	Findings
Kamei et al. [80]	56 HCV	9×10^6 IU daily for 4 weeks; then 3×/week for 20 weeks	QEEG	(1) Baseline (2) Treatment week 2 (3) Treatment week 4 (4) End of treatment	Diffuse slowing during treatment that reversed after treatment ended
Kamei et al. [81]	56 HCV	9×10^6 IU daily for 4 weeks; then 3×/week for 20 weeks	(1) QEEG (2) Cognitive screening measure (3) Clinician-administered measures of depression and anxiety	(1) Baseline (2) Treatment week 2 (3) Treatment week 4 (4) End of treatment	Cognitive screening scores fell 2–5 points at weeks 2 and 4; reduction in mental calculations, orientation, and recall, which reversed after treatment ended; QEEG changes related to cognitive scores but not depression or anxiety scores
Kamei et al. [90]	98 HCV	9×10^6 IU daily for 4 weeks; then 3×/week for 20 weeks	QEEG	(1) Baseline (2) Treatment week 2 (3) Treatment week 4 (4) End of treatment	Increased slow waves and decreased alpha 2 and beta waves during treatment; alterations increased with age
Juengling et al. [82]	11 HCV	3–6 MU 3×/week	(1) PET (2) Cognitive tests of verbal fluency, learning, retention, attention, psychomotor speed, and mental flexibility (3) Self-report measures of depression, anxiety, and global emotional distress	(1) Baseline (2) After 3 months of treatment	After 3 months of treatment, hypometabolism in bilateral prefrontal area and R parietal cortex and hypermetabolism in bilateral putamina (L > R), posterior R thalamus, and L occipital area; Deficits in learning; No significant changes in depression, anxiety, or global emotional distress but depression score related to hypometabolism in L frontal area
Hilsabeck et al. [83]	11 HCV treated 19 HCV untreated	1.5–5 MU 1×/week of PEG intron ($N = 7$) or 180 μg 1×/week of PEGASYS ($N = 4$) and 400–1,200 mg/day of ribavirin ($N = 11$)	Cognitive tests of attention, psychomotor speed, and mental flexibility	(1) Baseline (2) After at least 2 months of treatment (range 2–6 months)	Treated patients significantly slower than untreated patients at time 2 on a measure of mental flexibility; IFN-α may interfere with ability to benefit from practice
Amodio et al. [84]	20 HCV	3 or 6 MU 3×/week and 15 mg/kg/day ribavirin	(1) EEG (2) P300 (3) Cognitive tests of psychomotor speed, arousal, memory, attention, perception, verbal fluency, visual-spatial abilities, and executive functions (4) Clinician-rated measures of depression and anxiety (5) Self-report measures of depression and anxiety	(1) Baseline (2) After 2 months (3) After 6 months	EEG mean dominant frequencies decreased in parietal derivations and α band activity increased in frontal derivations after 6 months of treatment; No changes in P300 or cognitive test performance over time; Clinician-rated but not self-reported depression and anxiety increased after 2 months and was independent of EEG changes

Table 2 continued

Study	Sample	IFN dose	Measures	Assessment intervals	Findings
Capuron et al. [85]	10 HCV treated 11 HCV untreated	1.5 MU 1×/week of PEG intron and 800–1,400 mg/day of ribavirin	(1) fMRI (2) Cognitive test of reaction time and visuospatial attention (3) Clinician-administered measure of depression	Treatment week 12	Activation greater in L anterior cingulate cortex of treated group, which was highly correlated with number of errors on the cognitive task; No group differences on the cognitive task and no relationship between activation and complaints of loss of concentration or fatigue
Kraus et al. [86]	70 HCV	5 MIU 3×/week of IFN-α-2b ($N = 38$) or 80–150 μg 1×/week of PEG IFN-α-2b ($N = 32$) for 6 or 12 months depending on genotype and 800–1,200 mg/day of ribavirin	(1) Cognitive tests alertness, divided attention, vigilance, and working memory (2) Self-report measures of depression and anxiety	(1) Baseline (2) Treatment week 4 (3) After 3–4 months (4) After 6–8 months (5) 4–6 weeks after treatment completion	77% of patients deteriorated on at least one measure and could not be characterized based on pretreatment variables; reaction times increased but returned to baseline after treatment ended; no relationship between cognitive deterioration and depression, anxiety, or fibrosis stage; weak relationship between cognitive deterioration and drop in hemoglobin
Reichenberg et al. [88]	50 HCV	PEG IFN-α and ribavirin (doses not specified)	(1) Self-report measure of depression (2) Verbatim complaints of cognitive problems	(1) Baseline (2) Treatment week 1 (3) Treatment week 2 (4) Treatment week 4 (5) Every 4 weeks during treatment (6) After treatment at weeks 4, 8, 12, and 24	No reports of cognitive problems at baseline; 30% reported cognitive problems during treatment; 16% reported continued cognitive problems 8 weeks after end of treatment; No relationship between depression during treatment and subjective cognitive complaints
Lieb et al. [87]	33 HCV 4 HBV 1 HCV/HBV	3–6 MIU 3×/week ($N = 32$; 3 also treated with 1,200 mg/day ribavirin) or 180 μg 1×/week of PEG IFN-α ($N = 6$)	(1) Cognitive tests of verbal fluency, learning, retention, attention, psychomotor speed, and mental flexibility (2) Self-report measures of depression, anxiety, and global emotional distress	(1) Baseline (2) Treatment week 12	Immediate recall and verbal fluency decreased after 12 weeks of treatment; cognitive deterioration not related to depression or anxiety

IFN, Interferon-alpha; QEEG, Quantitative electroencephalogram; PET, positron emission tomography; R, right; L, left; fMRI, functional magnetic resonance imaging; PEGASYS, peginterferon alfa-2a; PEG intron, recombinant interferon alpha, subtype 2b, and polyethylene glycol

Table 3 Studies of cognitive dysfunction in HCV patients co-infected with HIV

Study	Sample	Sample characteristics	Measures	Findings
Von Giesen et al. [95]	44 HCV 43 HIV 43 co-infected	IVDU = 18% HCV; 63% HIV; 63% co-infected Mean CD4 = 357 in HIV; 326 in co-infected ART = 2% HIV; 42% co-infected	(1) Cognitive tests of intelligence, attention, and memory (2) Screening test for HIV dementia (3) Self-report measures of psychiatric and somatic symptoms (4) Clinician-administered measure of depression (5) Electrophysiologic motor tests	Reaction time slower in co-infected group; No group differences in cognitive performances; HCV patients endorsed fewer affective disorders and were less depressed than HIV or co-infected patients; No effect of IVDU
Ryan et al. [96]	49 HIV 67 co-infected	IVDU = Not reported Mean CD4 = 142 in HIV; 165 in co-infected ART = Not reported	(1) Cognitive tests of psychomotor speed, attention, learning, memory, verbal fluency, executive function, and premorbid functioning (2) Psychiatric diagnostic interview	Co-infected patients more impaired in executive functioning and more likely to meet criteria for AIDS dementia complex; More co-infected patients have histories of opiate, cocaine, or stimulant dependence; No group differences in rates of primary mental disorders
Martin et al. [97]	20 HCV 39 HIV 28 co-infected 69 controls	IVDU = 85% HCV; 34% HIV; 86% co-infected; 36% controls Mean CD4 = 498 in HIV; 495 in co-infected ART = 66% in HIV; 81% in co-infected	Computerized cognitive test of reaction time and response inhibition	HIV patients impaired primarily on "executive" component while HCV patients showed overall slowed information processing; Possible additive effect of HCV and HIV on cognitive dysfunction
Perry et al. [94]	47 HCV 29 co-infected	IVDU = Not reported Mean CD4 = 479 ART = 51%	Cognitive tests of attention, psychomotor speed, and mental flexibility	No group differences in cognitive performances but a greater percentage of HCV patient were impaired on 2 or more measures; Greater fibrosis related to greater impairment
Clifford et al. [98]	234 HIV 30 co-infected	IVDU = 4% HIV; 47% co-infected Mean CD4 = 251 in HIV; 299 in co-infected ART = Not reported	(1) Cognitive tests of attention, psychomotor speed, and mental flexibility (2) Self-report measures of depression, sleep, anxiety, and somatic symptoms	Co-infected patients performed worse on cognitive tests than HIV-infected patients; Co-infected patients more depressed but not more anxious (sleep problems and somatic symptoms were marginally more severe in co-infected)
Richardson et al. [99]	27 HCV 75 HIV 70 co-infected 48 controls (all participants were women)	Lifetime high drug use = 52% HCV; 15% HIV; 63% co-infected; 13% controls Mean CD4 = 1,006 HCV; 376 HIV; 437 co-infected; 1,260 controls ART = Not reported	(1) Cognitive tests of learning, recall, divided attention, mental flexibility, and psychomotor speed (2) Self-report measure of depression	39% cognitively "abnormal," with greater prevalence of cognitive dysfunction in HCV positive women; Co-infected women had substantially increased odds of cognitive dysfunction; No group differences in self-reported depression

Table 3 continued

Study	Sample	Sample characteristics	Measures	Findings
Cherner et al. [100]	347 HIV	METH use last 30 days = 18% HIV; 22% co-infected	Cognitive tests of verbal fluency, learning, recall, attention/working memory, information processing speed, abstraction/problem solving, and motor ability	HCV infection has an independent negative effect on cognitive functioning and the effects of HCV, HIV, and METH use are additive
	83 co-infected	Mean CD4 = 467 in HIV; 418 in co-infected ART = 95% HIV; 93% co-infected		
Letendre et al. [101]	414 HIV	METH dependent = 39% HIV; 70% co-infected	Cognitive tests of verbal fluency, learning, recall, attention/working memory, information processing speed, abstraction/problem solving, motor ability, and premorbid intelligence	Co-infected patients exhibited greater global cognitive dysfunction, which was independent of METH dependence; Weak relationship between impaired memory and HCV viral load; HCV infection associated with higher immune activation
	112 co-infected	Mean CD4 = 422 in HIV; 356 in co-infected ART = 58% HIV; 62% co-infected		

HIV, Human immunodeficiency virus; IVDU, intravenous drug use; ART, antiretroviral therapy; AIDS, acquired immune deficiency syndrome; METH, methamphetamine

preted these findings as evidence that "HCV injures the CNS independently of two important comorbidities, HIV and methamphetamine" (pS76). In addition, a weak relationship between HCV viral load in plasma and memory impairment was suggested, and HCV infection was associated with higher levels of TNF-α and monocyte chemotactic protein (MCP)-1, a protein that has been implicated in the pathogenesis of HIV-associated dementia [102].

Implications and future directions

In summary, cognitive impairment has long been associated with chronic liver disease, although it was believed to occur mainly in patients with decompensated cirrhosis. Recent research has demonstrated that cognitive deficits are apparent in HCV patients with and without cirrhosis. Approximately one-third of HCV-infected patients exhibit cognitive deficits, with the likelihood of impairment increasing with the presence of greater levels of fibrosis and medical comorbidities, such as HIV. Attention, concentration, and psychomotor speed are the cognitive functions most likely to be impaired, suggesting a proclivity for frontal-subcortical systems. Antiviral therapy with IFN-α also may result in cognitive dysfunction, again showing a tendency to affect frontal-subcortical circuits preferentially.

While the etiology of cognitive impairment in HCV remains unknown, converging evidence suggests that the contributions of premorbid personality characteristics and lifestyle choices, psychiatric disease and emotional distress, and direct effects of the virus are minimal. Further investigation of the role of chronic immune system activation, particularly the cytokine cascade, is needed and may shed light on possible avenues for intervention. This line of work is especially relevant because of the increasing move toward using biological agents like IFN-α in the therapy of human diseases [103]. The role of genetics is also likely to be a key component, as one group of researchers reported increased susceptibility to and variability in neuropsychiatric symptoms during IFN-α therapy in HCV patients with an apolipoprotein E (APOE) ε4 allele [104]. In addition, Adair and colleagues [105] found the down-regulation of several genes important in terms of oxidative phosphorylation and protein translation in HCV-positive patients compared to controls. Oxidative phosporylation is the primary source of energy for all cells, and impaired energy metabolism in the brain has been hypothesized to be a leading cause of disorders resulting in cognitive dysfunction [106].

The clinical manifestation of these cognitive deficits is another important area of study. It has been shown that

quality of life (QOL) is significantly reduced among people with HCV, independent of the severity of liver disease [107]. Although preliminary data do not suggest a significant relationship between QOL and cognitive deficits [10, 108], more research is needed to understand how cognitive deficits may affect daily life, such as work productivity and medical adherence which, in turn, may affect QOL. For example, cognitive impairment has been associated with poorer medication adherence in persons with HIV and older adults [109, 110]. These data highlight the need for careful assessment of the disabling factors (cognitive, psychiatric and social) that impact the well-being of HCV patients. Future studies are needed to delineate the multiple and interrelated factors that impact the functioning of people with HCV.

Another area of increasing interest is the combined effect of aging and cognitive deficits in HCV. As the HCV population grows older, existing cognitive deficits may interact with the aging process to impair functioning earlier and/or manifest in neurodegenerative disorders, such as Alzheimer's disease or vascular dementia sooner. Aging may interact with antiviral therapy [90] or co-infection with HIV [99] to increase susceptibility to cognitive dysfunction. Longitudinal studies will be needed to explore the possibility of HCV-associated cognitive dysfunction as a risk factor for age-related decline.

In closing, cognitive problems such as those experienced by HCV patients may influence medical care, as cognitively impaired patients may fail to remember (or remember incorrectly) important details about their disease, treatment regimen, and/or physicians' recommendations. They may experience difficulties performing household and job duties as efficiently and accurately as before, leading to frustration and distress, which can contribute to mood disturbances and exacerbate cognitive complaints. Thus, cognitive dysfunction is an important problem for persons with chronic HCV as it may interfere with effective disease management and contribute to increased morbidity and disability. Given the prevalence and significant impact of cognitive dysfunction in HCV, future research needs to target prevention and management of cognitive difficulties, in addition to other virus-related complications.

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