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Impairments in Fine-Motor Coordination and Speed of Information Processing Predict Declines in Everyday Functioning in Hepatitis C Infection

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Abstract

Research increasingly supports the neurovirulence of chronic infection with the hepatitis C virus (HCV). For example, HCV infection has been associated with neuropsychological impairment in several ability areas, including psychomotor skills. This study aimed to examine whether HCV-associated neuropsychological impairment is predictive of declines in the independent performance of physical (PADLs) and instrumental (IADLs) activities of daily living. One-hundred and six volunteers with HCV infection completed a comprehensive neuropsychological, medical, and psychiatric research evaluation. As compared to 30 HCV seronegative comparison subjects, the HCV-infected group reported significantly greater declines in both PADLs and IADLs. Within the HCV cohort, individuals with impaired speed of information processing reported significantly greater IADL declines, whereas impaired fine-motor coordination was associated with declines in both IADLs and PADLs. In a series of regression analyses, impaired speed of information processing and depressive symptoms (as measured by the Beck Depression Inventory) were the only independent predictors of IADL declines, whereas general affective distress (as measured by the Profile of Mood States), sex, and fine-motor coordination impairment were predictive of declines in PADLs. Although the clinical assessment of HCV typically emphasizes both affective (e.g., depression) and physical factors, findings from the present study suggest that cognitive impairment is an important contributor to everyday functioning in persons living with HCV infection and therefore warrants consideration in clinical and research evaluations.

Keywords

hepatitis; cognitive impairment; depression; activities of daily living; motor

Hepatitis C Virus (HCV) is a single-stranded RNA flavivirus that affects approximately 3 million adults in the United States and is commonly associated with chronic liver disease. Research increasingly supports the neurovirulence of chronic HCV infection: HCV RNA is detectable in brain parenchyma (Radkowski *et al.*, 2002) and HCV antigens have been detected

in the frontal cortex, white matter, and basal ganglia of HCV-infected persons (Letendre *et al.*, 2007). In particular, Letendre and colleagues (2007) report that HCV immunoreactivity in the CNS was mainly associated with astroglia. It is hypothesized that the mechanism of HCV neurotoxicity involves the interaction of this HCV antigen with host cellular proteins, resulting in an alteration of these pathways, and eventually leading to cell death and/or abnormal inflammatory responses (Letendre *et al.*, 2007). In addition, imaging studies have reported evidence of elevations in metabolic markers of neuronal injury and neuroinflammation in the basal ganglia, frontal cerebral white matter, and occipital grey matter of HCV-infected individuals (Forton *et al.*, 2005; Weissenborn *et al.*, 2004).

There is also emerging evidence in the literature supporting the association between HCV infection and cognitive deficits (see Forton *et al.*, 2005, for a review). Approximately 40-50% of HCV infected individuals may be cognitively impaired (Bieliauskas *et al.*, 2006; Hilsabeck, Hassanein, Carlson, Ziegler, & Perry, 2003). Although findings are somewhat mixed across studies (e.g., Soogoor *et al.*, 2006), the literature suggests that HCV may be associated with impairments in the areas of motor skills (Cherner *et al.*, 2005; Cordoba *et al.*, 2003; Ryan *et al.*, 2004), attention/working memory (e.g., Cordoba *et al.*, 2003), speed of information processing (e.g., Cherner *et al.*, 2005), executive functions (Bieliauskas *et al.*, 2006), and episodic memory (e.g., McAndrews *et al.*, 2005). Such variability in the literature could be partly explained by the nascent nature of this area of investigation and inconsistency in neuropsychological assessments and methodologies across studies. In addition, endemic factors in the HCV infected population (e.g., HIV co-infection, substance abuse) could make it difficult to assess the independent effect of HCV on neuropsychological impairment. Other factors reported to be related to HCV-associated neuropsychological impairment include depression (e.g., Fontana *et al.*, 2005) and several HCV-associated disease characteristics (e.g., liver fibrosis and HCV-RNA levels; Hilsabeck *et al.*, 2003; Letendre *et al.*, 2005). Nevertheless, research from our own group has shown that even after controlling for potentially confounding comorbidities (e.g., substance abuse), HCV was significantly associated with cognitive impairment in patients co-infected with HIV (Cherner *et al.*, 2005).

HCV can also lead to marked disability, particularly in the late stage of the disease. For example, significant declines in physical and mental health-related quality of life (HRQL; i.e., perceived health concerns and their impact on important life roles) are observed in many HCV-infected individuals (Cordoba, *et al.*, 2003; Hussain *et al.*, 2001). This decline in HRQL may even appear in the early, less severe stages of disease (Foster, Goldin, & Thomas, 1998). Nevertheless, other relevant factors, such as medical comorbidities, depression, and HCV-associated stigma, have been linked to declines in HRQL (Forton *et al.*, 2005). Considering the HIV literature (e.g., Heaton *et al.*, 2004), one might hypothesize that HCV-related neuropsychological impairment may also be associated with poorer HRQL and decrements in general everyday functioning (i.e., the physical and mental skills required for independent living) in persons infected with HCV. To our knowledge, however, only five previous studies have examined the association between neuropsychological impairment and everyday functioning in HCV, all of which have focused exclusively on HRQL. Three studies reported no significant associations between neuropsychological impairment and HRQL (Cordoba *et al.*, 2003; Forton, *et al.*, 2002; Thein *et al.*, 2007), while two others demonstrated that greater functional decline corresponded with neuropsychological impairment (Bieliauskas *et al.*, 2006; Bieliauskas *et al.*, 2007). For example, Bieliauskas and colleagues (2006) reported that individuals deemed cognitively impaired self-reported lowered overall HRQL, when compared to a healthy U.S. population sample.

Several notable limitations hamper interpretation of the emergent literature on neuropsychological impairment and everyday functioning in HCV. For instance, no prior studies have fully considered the confounding influence of substance abuse, emotional distress,

liver disease characteristics, and demographics. In addition, prior studies in HCV examining the relationship between functional declines and neuropsychological impairment have typically utilized generic HRQL measures (e.g., SF-36 Health Survey; Ware, Gandek, & The IQLA Project Group, 1994), whose strengths lie in their ability to characterize an individual's perception of their level of general health and sense of well-being. However, such generic instruments also have limitations; for example, they do not capture other important aspects of everyday functioning (e.g., the skills necessary for independent living). Furthermore, they provide a somewhat static assessment of an individual's perception of their current functioning, which is important because medical conditions like HCV infection may lead to *declines* in everyday functioning (e.g., shopping, bathing), even if individuals have premorbid difficulties in these areas. Therefore, one could theoretically increase the sensitivity and specificity of everyday functioning measurements by comparing an individual's current performance of activities of daily living (ADLs) with their premorbid (or best) performance.

Considering the limitations of the existing literature, the aim of the current study was to evaluate the cognitive predictors of ADL declines in HCV, giving due attention to other possibly confounding factors. We hypothesized that cognitive impairment would be significantly associated with a decline in ADL functioning after controlling for demographics and possible drug and liver disease confounds. Finally, since it has been shown that affective distress is common among HCV-infected individuals (Dwight *et al.*, 2000), we expected ADL decline to be related to psychiatric disturbance (e.g., depressive symptoms). Based on the HIV literature (e.g., Heaton *et al.*, 2004), we hypothesized that both affective distress and neuropsychological impairment would be independently predictive of ADL declines.

Methods

Participants

HCV participants included 106 volunteers who were recruited consecutively and prospectively enrolled in NIDA-funded projects on the combined central nervous system effects of methamphetamine, HIV, and HCV infection. In an effort to isolate the independent effects of HCV on neurocognition, individuals with histories of severe psychiatric illness (e.g., schizophrenia), HIV infection, or neurological disease (e.g., seizure disorders) were excluded from the current study, as were individuals meeting *DSM-IV* criteria for other substance abuse (i.e., sedatives, cocaine, opioids, hallucinogens, and inhalants) in the year prior to their study visit. Likewise, those individuals meeting *DSM-IV* criteria for alcohol dependence within 12 months of evaluation or substance dependence (i.e., sedatives, cocaine, opioids, hallucinogens, and inhalants) within 5 years of evaluation were excluded. We did not exclude participants with histories of marijuana- or methamphetamine-related disorders, as use of these drugs is highly prevalent within this population. In order to confirm recent abstinence, urine testing for common recreational drugs was performed at the time of the study visit using the Rapid Drug Screen (Pharmatic Inc., San Diego, CA). HCV serostatus was determined retrospectively by standard clinical antibody detection. Blood was collected by venipuncture. HCV RNA was measured in serum using RT-PCR (NGI SuperQuant; National Genetics Institute, Los Angeles, CA, USA; nominal detection limit of 100 IU/mL).

The demographic and clinical characteristics of the study participants are presented in Table 1. Our study cohort was predominantly male, Caucasian, middle-age, and high school educated. A small minority met *DSM-IV* criteria for current major depression, while over one in three had met criteria during their lifetime. Global cognitive impairment was observed in close to half of the HCV+ participants. None of the participants reported current or past treatment for HCV and serum HCV-RNA concentrations varied widely. Few of our participants had liver biopsy data available; indicating that for many in our study cohort, liver disease was not considered severe enough by their clinician to consider therapy. During physical exams,

conducted as part of the research evaluation, there was an absence of signs of advanced liver disease (e.g., jaundice, ascites, or asterixis). The median for the AST (aspartate aminotransferase) to platelet ratio index, a marker of liver disease severity, was in the range indicating mild disease severity, as were other indices of hepatic function (e.g., bilirubin). As might be expected, there was a high prevalence of lifetime DSM-IV diagnoses of substance-related disorders (see Table 2).

In addition, 30 HCV seronegative participants enrolled in a separate NIMH-funded project were included to serve as a demographically-matched comparison group. Although this cohort underwent a different psychiatric and neuropsychological evaluation than the HCV group, they were subject to the same exclusion criteria described above and completed the Lawton & Brody (1969) ADL questionnaire (described below). As shown in Table 1, the seronegative comparison group did not differ from the HCV+ group in terms of age, ethnicity, or sex (p s > .10), but reported significantly more years of education (p < .05). In order to assess for mood and substance use disorders, HCV seronegative participants were administered the Composite International Diagnostic Interview (CIDI, Robins et al., 1988). This computer-assisted lay-administered instrument has been reported to have strong concordance with the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & William, 1996; Kessler et al., 1998). Rates of substance use disorders, but not major depression, were lower in the HCV seronegative group (see Tables 1 and 2).

Procedure

All HCV+ participants were administered a neuropsychological test battery covering several cognitive domains (for a detailed description see Rippeth *et al.*, 2004). In brief, the ability domains assessed and their respective administered tests were: (a) Verbal Fluency - Letter Fluency (FAS) and Category Fluency (animals) (Borkowski, Benton, & Spreen, 1967); (b) Working Memory - Paced Auditory Serial Addition Task (Gronwall, 1977) and Wechsler Adult Intelligence Scale-III (WAIS-III) Letter-number Sequencing (Psychological Corporation, 1997); (c) Speed of Information Processing - WAIS-III Digit Symbol, WAIS-III Symbol Search (Psychological Corporation, 1997), Trail Making Test, Part A (Reitan and Davidson, 1974), and Stroop Color and Word Test (color trial; Golden, 1974); (d) Learning - Heaton Story Memory Test (Heaton, Grant, & Matthews, 1991), Hopkins Verbal Learning Test-Revised (HVLT-R) Trials 1-3 (Benedict, Schretlen, Groninger, & Brandt, 1998); Heaton Figure Memory Test (Heaton *et al.*, 1991), and Brief Visuospatial Memory Test-Revised Trials 1-3 (BVMT-R; Benedict, 1997); (e) Recall - Delayed free recall trials of the HVLT-R, BVMT-R, and Heaton Story and Figure Memory Tests; (f) Executive Functions - Wisconsin Card Sorting Test (64-item version; Kongs, Thompson, Iverson, & Heaton, 2000), Halstead Category Test (Halstead, 1947), Trail Making Test, Part B, and Stroop Task interference ratio; and (g) Fine-motor Coordination - Grooved Pegboard Test (Klve, 1963) dominant and nondominant hand performances. Raw scores were converted to demographically-adjusted T-scores, which were used to generate domain-specific clinical ratings of neuropsychological functioning (Woods *et al.*, 2004). Participants with a clinical rating above 4 (which approximates using a < 40 T-score cutoff) were classified as impaired (see Woods *et al.*, 2004, for details regarding the interrater reliability and construct validity of this methodology).

HCV+ participants also completed the Beck Depression Inventory-I (BDI-I; Beck & Steer, 1987), Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1971), the SCID, and a modified version of the Lawton and Brody (1969) ADL scale. The BDI-I is a 21-item self-report measure that rates severity of depressive symptoms during the past week, addressing somatic (e.g., weight loss, fatigue) and non-somatic (e.g., suicidal ideation, feelings of guilt) depressive symptoms - higher scores indicate greater depressive symptomatology. The POMS is a self-report measure assessing mood states over the past seven days. It is made up of 65

descriptors (e.g., friendly, muddled) rated on a five-point scale (from 0 = not at all, to 4 = extremely). In this study, the POMS Total Score was used in all analyses, with higher scores indicating greater general affective distress. The SCID is a semi-structured clinician-administered interview using *DSM-IV* criteria to identify major psychiatric disorders. Interviewers (staff psychologists, postdoctoral clinical psychology fellows, or advanced clinical psychology doctoral students) were trained to a criterion standard.

In the present study we used a modified version of Lawton and Brody's (1969) ADL scale, which has been used extensively in HIV infection research (see Heaton *et al.*, 2004; Woods *et al.*, 2006; Woods *et al.*, in press). The ADL scale consisted of items detailing the degree to which individuals independently function in 12 different areas related to daily tasks. Seven IADL (i.e., higher-level living skills) items assessed functioning in managing finances, groceries, cooking, transportation, shopping, medication management, and employment. Similarly, five PADL (i.e., more basic physical and self-maintenance skills) items assessed functioning in the areas of housekeeping, home repairs, bathing, dressing, and laundry. For each activity related to an area of functioning, participants separately rated their current and highest (previous) level of functioning (or independence). Items in the ADL scale are constructed so that a higher score in each item indicates poorer functioning and are rated on either a four-point scale (0 to 3) or a three-point scale (0 to 2). The range of possible scores is 0 to 13 for the PADL subscale and 0 to 17 for the IADL scale. When an individual rated their current level of functioning lower than their best past level, this is considered an indication of ADL decline. For our analyses, we summed the difference between current and highest level of functioning for each area and separately for IADL and PADL items (see Table 3). Thus, this allowed us to examine decline in IADLs and PADLs as a continuous variable, where higher scores indicate a more severe reported decline in current versus past functioning. Overall, functional declines were generally comparable prevalent across domains in the HCV+ group, with a slightly greater decline in the area of employment (see Table 3).

Statistical Analyses

The primary dependent variables of interest were all non-normally distributed as assessed with the Shapiro-Wilk *W* test (all *ps* < .05). Accordingly, all subsequent analyses were undertaken using a nonparametric approach, including Wilcoxon Rank Sums test for between-group comparisons and Spearman's ρ for correlational analyses. In addition, any variables that proved to be significantly associated with ADL decline were analyzed as predictors in a least squares regression (although the data were marginally non-normal, a check of the linear regression residuals nevertheless showed no serious departures from normality in their distributions and therefore they were deemed appropriate). The Cohen's *d* statistic was used to measure the effect sizes of the group comparisons. By convention, *d*-values of 0.2, 0.5, and 0.8 correspond to small, medium, and large effect sizes, respectively (Cohen, 1988). The critical alpha level was set at the standard 0.05 value for all statistical analyses, which were performed using JMP software (version 6.0, SAS Institute, Cary, NC, USA).

Results

As shown in Table 3, the severity of PADL and IADL declines was significantly greater in the HCV+ cohort as compared to the healthy seronegative comparison group (*ps* < 0.05; *ds* = 0.52 and 0.66, respectively). Given that the HCV+ group had achieved fewer years of education and evidenced lower rates of major depression and substance use disorders, a follow-up linear regression analysis was conducted to examine the effect of HCV on PADLs and IADLs while considering the possible confounding effects of these variables. The regression analyses, which included HCV serostatus, history of major depression, history of substance use disorder, and

education as predictors, revealed that HCV serostatus was the only significant, independent predictor of PADLs ($p = .02$) and IADLs ($p = .008$).

With regard to the predictors of ADL declines within the HCV+ group ($N = 106$), demographic factors (age, education, and ethnicity) were not significantly associated with either IADL or PADL decline (all $ps > 0.10$). However, there was a significant relationship between sex and PADLs, with women reporting greater declines than men ($\chi^2 = 4.03$, $p = 0.045$). Sex was not associated with IADLs ($p > .10$). We also analyzed the possible effect of HCV-related clinical characteristics on ADL declines utilizing Spearman's ρ tests. As shown in Table 4, none of the markers of liver disease were associated with PADL or IADL decline ($ps > .10$).

As concerns psychiatric predictors of ADL declines in the HCV+ cohort, substance abuse/dependence was not significantly related to either IADL or PADL declines (all $ps > 0.10$). However, a series of nonparametric Spearman's ρ tests indicated that the decline in PADLs and IADLs correlated significantly with BDI-I ($\rho = 0.42$ and 0.58 , respectively, $ps < 0.001$) and POMS Total ($\rho = 0.42$ and 0.51 , respectively, $ps < 0.001$). Regarding the BDI findings, both somatic and non-somatic symptoms of depression were comparably associated with PADLs ($\rho = 0.30$ and 0.41 , respectively, $ps < 0.01$); however, non-somatic symptoms were slightly better correlated with IADLs ($\rho = 0.61$, $p < 0.001$) than were somatic symptoms ($\rho = 0.40$, $p < 0.001$). The possible effect of a current diagnosis of Major Depressive Disorder (MDD) could not be evaluated as the number of participants meeting criteria was limited. However, lifetime history of MDD diagnosis was not found to be significantly related to either IADL or PADL declines (all $ps > 0.10$).

Global cognitive impairment was not associated with IADL decline, but was associated with greater PADL decline ($\chi^2 = 3.98$, $p = 0.046$, $d = .33$). Analysis of specific cognitive domains showed that those individuals categorized as impaired in fine-motor coordination reported higher decline in PADLs when compared to those who performed within normal limits in that domain ($p < 0.05$; $d = 0.83$). In terms of IADL decline, only individuals impaired in speed of information processing and fine-motor coordination reported significantly higher declines when compared to individuals categorized as cognitively normal in those domains ($ps < 0.05$; $d = 0.74$ and 0.67 , respectively). Please refer to Figures 1 and 2, where the y-axis represents average IADL or PADL decline scores, with separate bars for the impaired (striped bars) and normal (gray bars) groups for each of the seven cognitive domains shown on the X axis. As can be seen, all significant between group differences were associated with rather large effect sizes (range = $0.67 - 0.83$). There was no effect of impairment in verbal, working memory, learning, recall, or executive functions on either IADLs or PADLs ($ps > .10$).

In a regression analysis that included clinical ratings of impairment in speed of information processing and fine-motor coordination, along with POMS and BDI-I total scores, the overall model accounted for a significant amount of variance in IADL decline ($R^2 = 0.30$, $F(4, 105) = 10.64$, $p < 0.0001$). However, the only independent predictors of IADL decline were BDI-I total scores and impairment in speed of information processing ($F(1, 105) = 4.12$, $p = 0.04$ and $F(1, 105) = 4.26$, $p = 0.04$, respectively). In a separate regression analysis including global impairment, clinical ratings of fine-motor coordination, POMS total, BDI-I total, sex, and with PADL decline as the criterion, the overall model again accounted for a significant amount of variance ($R^2 = 0.33$, $F(5, 105) = 7.30$, $p < 0.001$). Impairment in fine-motor coordination and POMS total score ($F(1, 105) = 4.36$, $p = 0.04$ and $F(1, 105) = 7.18$, $p = 0.01$, respectively) proved to be the only significant independent predictors of PADL decline. In addition, sex was an independent predictor of PADL decline ($F(1, 105) = 6.06$, $p = 0.02$). Note that, regression results did not differ when either the somatic and non-somatic scales of the BDI were used instead of total score.

Finally, a series of post-hoc analyses were conducted to examine the potential effects of fatigue, which is a major issue in the HCV-infected population that may be associated with functional declines and poorer HRQL (Hilsabeck, Hassanein, & Perry, 2005). In fact, the POMS fatigue scale was correlated with both PADLs ($\rho = 0.37, p < 0.001$) and IADLs ($\rho = 0.39, p < 0.001$). However, a follow-up regression analyses predicting PADLs from the POMS fatigue scale, BDI-I total, fine-motor coordination impairment, and sex, only the BDI-I ($p = 0.009$) and motor impairment ($p = 0.009$) survived as significant independent predictors. Similar results were observed for the IADL scale regression, which showed significant effects for the BDI-I ($p = 0.0002$) and speed of information processing domain ($p = 0.03$), but not fine-motor coordination or the POMS fatigue scale. (N.B.: The POMS total was not included in either of these analyses due to collinearity [$\rho > 0.9$] with the fatigue scale).

Discussion

Recent data indicate that HCV infection is associated with neuropsychological impairment. In this study we aimed to assess the relationships between HCV-associated cognitive deficits and declines in everyday functioning. Findings revealed that HCV infection was associated with modest, but statistically significant declines in both PADLs and IADLs as compared to healthy, seronegative comparison subjects. Group differences persisted even when the possibly confounding effects of substance-related disorders, depression, and demographics (i.e., education) were included in the statistical model. Overall, the magnitude of the ADL declines in this relatively healthy HCV cohort corresponds to a medium effect size, but only 18% of the sample evidenced 2 or more areas of decline, which is the traditional definition of “dependence” (e.g., American Psychiatric Association, 1994; Woods et al., 2006). Indeed, the prevalence and severity of ADL dependence and declines in HCV was slightly less than is typically observed using similar methodologies in the HIV-infected population (Heaton et al., 2004; Sadek et al., 2007; Woods et al., 2006).

Nevertheless, consistent with a priori hypotheses, results revealed that neuropsychological impairment was associated with and may increase the risk of IADL and PADL declines. Consistent with the HIV literature (e.g., Marcotte *et al.*, 1999; Woods *et al.*, 2006), deficits in speed of information processing and fine-motor coordination were related to greater declines in ADL performance among HCV-infected individuals. In other words, individuals with slowed cognitive and psychomotor functions experience greater difficulty keeping pace with the considerable demands of independently performing normal daily tasks (e.g., managing finances and medication adherence). Interestingly, impairment in fine-motor coordination was a stronger predictor of declines in PADLs, whereas impaired speed of information processing related more closely to IADL decline. These results are commensurate with findings in Parkinson's disease; for example, Cahn and colleagues (1998) reported on the unique contribution of cognitive and motor functioning to ADLs in Parkinson's disease patients. Specifically, IADL performance was selectively related with set-shifting ability (as measured by Trails B) whereas PADL performance was related to fine motor control and speed (as measured by the Finger Tapping test). Similarly, findings from the present study revealed that individuals who performed poorly on neuropsychological tests requiring fine motor skills (i.e., grooved pegboard) reported a more difficult time in performing PADLs (e.g., bathing, laundry). On the other hand, individuals who were impaired on neuropsychological tests that involve quickly processing information in an efficient and accurate manner reported a greater decline in IADLs (e.g., managing finances, shopping). Therefore, the neuropsychological impairment observed in HCV can differently affect an individual's daily functioning depending on the particular area of cognitive impairment. For this reason, the assessment of HCV infected individuals and prediction of future functional decline must take into account not only the presence of neuropsychological deficits, but also the specific area impairment.

We cannot exclude the possibility that the speed of information processing finding, in particular, simply reflects reduced general cognitive efficiency in the HCV cohort. Arguing against this interpretation, however, are the largely null findings we observed for global cognitive status and other functional domains (e.g., working memory). Nevertheless, the clinical measures of processing speed used in this study were multifactorial and therefore future research is needed to evaluate which specific component processes of this construct (e.g., simple motor speed), if any, are driving the overall effect. For example, evaluation of theoretically-based measures of basic and complex reaction time (e.g., Martin *et al.*, 1999) may be informative in this population. Similarly, given our exclusive reliance on the Grooved Pegboard test as a measure of motor functions, future studies may wish to examine other specific motor skills, including finger tapping and grip strength, as well as more sophisticated and sensitive motor paradigms (e.g., motor programming; see Caligiuri & Buitenhuis, 2005). This is a particularly relevant avenue of research considering the known effects of HCV on the basal ganglia (e.g., Letendre *et al.*, 2007) and high prevalence of motor impairment in HCV-infected cohorts (e.g., Ryan *et al.*, 2004).

Findings from this study also support the idea that increased decline in the performance of ADLs is associated with greater depressive symptomatology, as measured by the BDI-I, and general affective distress, as measured by the POMS. That is, the functional declines observed in this study among HCV-infected individuals are strongly associated with concurrent emotional distress. Although fatigue, which is a notable feature of HCV infection, was correlated with ADL declines, it did not emerge as an independent predictor when evaluated against depressive symptoms and neuropsychological impairment (i.e., speed of information processing and fine-motor coordination). In fact, neither depressive symptoms nor general affective distress fully explain the report of functional decline in HCV. Impairments in fine-motor coordination and speed of information processing remained significant independent predictors of PADL and IADL declines, respectively, even when self-report measures of affective distress were considered in the statistical model. These findings are consistent with what has been reported in the HIV literature, where neuropsychological functioning and depressive symptoms are independent and significant predictors of ADLs (Heaton *et al.*, 2004). It appears that emotional distress and cognition each affect different aspects of ADL performance, in unique ways. Thus, evaluation of emotional distress, together with neuropsychological functioning is recommended for HCV infected individuals when deciding on appropriate disease management strategies.

Given the characteristics of our sample, we believe that our findings are fairly robust; however some limitations are worth noting. As reported above, our participants were treatment naïve and not currently undergoing anti-HCV treatment. Medical data regarding level of fibrosis were not available for our study cohort. Although the AST-to-platelet ratio index is a reasonable surrogate, future studies would benefit from inclusion of fibrosis information, when available. Moreover, in our study group the prevalence rates of common comorbid medical conditions in HCV (e.g. diabetes, hypertension, coronary artery disease) were quite low (i.e., less than 1%), which limits our ability to examine the importance of these factors as predictors of ADL functioning and also restricts the generalizability of our results. Nevertheless, the relatively mild HCV disease observed in our cohort likely represents a conservative bias and points to the importance of evaluating the relationships between cognitive, psychiatric, and functional outcomes in more severely affected cohorts in whom these factors may be exacerbated.

In addition, substance use related disorders were highly prevalent in our sample. While this might be more representative of “real world” individuals infected with HCV, one must consider the independent effect of substance use on functional decline and whether it is substance use-associated impairment, rather than HCV-associated impairment, that we observed. The focus of the funded project and the population from which we recruited our cohort (San Diego, CA),

resulted in high rates of methamphetamine use disorders among our study cohort. Numerous studies have shown that methamphetamine use uniquely contributes to NP impairment (e.g., Rippeth *et al.*, 2004), which in turn might lead to functional decline (e.g., Sadek et al., 2007). Nevertheless, substance use diagnoses were not predictive of either IADL or PADL declines in the current study. Another limitation of this study is the exclusion of persons with HIV infection, particularly considering that it has been estimated that at least 10% of HCV infected persons are coinfecting with HIV (Strader, Wright, Thomas, & Seef, 2004). This is important because one might expect the overall level of ADL declines, cognitive impairment, and affective distress to worsen in step with an increase in the number of co-morbid conditions (e.g., Cherner et al., 2005). A final important limitation to note is the type of assessment used in this study to measure functional decline, which consisted of a self-report measure that may be subject to bias. As such, future studies may wish to incorporate more objective functional outcomes, such as employment and the various performance-based functional tasks (see Heaton et al., 2004).

In summary, findings from this study revealed that individuals with HCV experience modest, but significant declines in both instrumental and physical activities of daily living, which are independently associated with impairment in speed of information processing and fine-motor coordination, respectively. In addition, affective distress was shown to be related to declines in everyday functioning. Given the association between typical HCV medical treatment and depression, the risk for functional decline in an otherwise “well-treated” individual can be high. Finally, these findings suggest that consideration of cognitive functioning, as well as affective (e.g., depression) and physical factors, are important in the clinical evaluation and treatment of individuals living with HCV infection. Likewise, research on HCV, including clinical trials, would benefit from the inclusion of neuropsychological and functional outcomes.

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Figure 1. Bar graph comparing mean IADL decline scores ($\pm$ SE) between HCV-infected individuals classified as impaired or normal on the seven cognitive domains. * $p < 0.05$

Figure 2.

Bar graph comparing mean PADL decline scores ($\pm$ SE) between HCV-infected individuals classified as impaired or normal on the seven cognitive domains. * $p < 0.05$

Table 1
Demographic and Clinical Characteristics of Study Cohort and Comparison Group

Variable	HCV+ (N=106)	HCV- (N=30)
Age <u>M</u> (<u>SD</u>)	46.5 (4.9)	43.2 (11.0)
Education <u>M</u> (<u>SD</u>) *	12.2 (2.7)	14.0 (2.1)
Ethnicity		
% Caucasian	77	62
% African-American	9	32
% Hispanic	9	0
% Other	4	6
Sex (% men)	61	60
Major Depression		
Current (%)	8	0
Past (%)	36	33
BDI-I Total Score <u>Median</u> (<u>IQR</u>)	10 (5, 17)	
POMS Total Score <u>Median</u> (<u>IQR</u>)	63 (32, 93)	
Globally Cognitively Impaired (%)	46	
HCV status (Medians, IQR)		Normal Values
HCV RNA, serum (log ₁₀ IU/mL)	5.8 (3.2, 6.4)	0
Total bilirubin (mg/dL)	0.7 (0.4, 0.9)	< 1.2
Albumin (g/dL)	4.0 (3.8, 4.2)	3.3-5.0
Ammonia (umol/L)	41.0 (30.0, 52.3)	11-35
AST-to-Platelet Ratio Index (APRI)	0.4 (0.3, 0.8)	< 1.5

* $p < .05$.

BDI-I = Beck Depression Inventory I; POMS = Profile of Mood States; HCV = Hepatitis C virus; AST = aspartate aminotransferase; IQR = inter quantile range

Table 2
Substance Use Disorders in Study Cohort and Comparison Group

Variable	HCV+ (N=106)	HCV- (N=30)
Any Substance Use Disorder		
Current	14	0
Past	86	57
Alcohol Use Disorder		
Current	3	0
Past	63	40
Cannabis Use Disorder		
Current	5	0
Past	57	23
Methamphetamine Use Disorder		
Current	8	0
Past	50	20
Cocaine Use Disorder		
Current	0	0
Past	43	20
Opioid Use Disorder		
Current	0	0
Past	31	3
Sedative Use Disorder		
Current	0	0
Past	19	10
Hallucinogen Use Disorder		
Current	0	0
Past	13	3

Note. Data are presented as population percentages. All of the study cohort participants with current alcohol use disorders met only abuse criteria.

Table 3
Lawton & Brody ADL Scale Decline Scores

Variable	HCV+ (N=106)	HCV- (N=30)
IADL Decline	0.8 (1.4)	0.0 (0.0)
PADL Decline	0.5 (1.0)	0.0 (0.2)
Number of Areas of IADL Decline	0.4 (0.8)	0.0 (0.2)
Number of Areas of PADL Decline	0.2 (0.6)	0.0 (0.2)
ADL Areas		
Managing Finances	0.1 (0.3)	0.0 (0.0)
Groceries	0.1 (0.3)	0.0 (0.0)
Cooking	0.1 (0.3)	0.0 (0.0)
Transportation	0.0 (0.2)	0.0 (0.0)
Shopping	0.1 (0.3)	0.0 (0.0)
Medication Management	0.1 (0.2)	0.0 (0.0)
Employment	0.4 (0.5)	0.0 (0.2)
Housekeeping	0.2 (0.4)	0.0 (0.0)
Home Repairs	0.2 (0.4)	0.0 (0.2)
Bathing	0.0 (0.0)	0.0 (0.0)
Dressing	0.0 (0.0)	0.0 (0.0)
Laundry	0.1 (0.2)	0.0 (0.0)

Note. Data represents means and standard deviations. ADL = activities of daily living; IADL = instrumental activities of daily living; PADL = physical activities of daily living

Table 4
Correlations (Spearman's ρ) Between HCV-related Clinical Characteristics and ADL Decline

Variable	IADL Decline	PADL Decline
HCV RNA	0.06	0.13
Total bilirubin	-0.18	-0.03
Albumin	-0.04	-0.04
Ammonia	-0.03	0.03
AST-to-platelet ratio index	-0.07	-0.04

Note. HCV = Hepatitis C virus; AST= aspartate aminotransferase; IADL = instrumental activities of daily living; PADL = physical activities of daily living. All $ps > 0.10$