HIGH LIGHT
CME

Hepatitis C augments cognitive deficits associated with HIV infection and methamphetamine

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Abstract—*Objective:* To examine the contribution of hepatitis C virus (HCV) infection to neurocognitive dysfunction in individuals with comorbid HIV infection or methamphetamine (METH) dependence. *Methods:* Neurocognitive functioning was examined in 430 study participants who were either normal controls or had HCV infection, HIV infection, history of METH dependence, or combinations of these factors as risks for cognitive deficits. *Results:* Rates of global and domain-specific neuropsychological (NP) impairment increased with the number of risk factors. HCV serostatus was a significant predictor of NP performance both globally and in the areas of learning, abstraction, and motor skills, with trends in speeded information processing and delayed recall. HCV serostatus did not predict scores in attention/working memory or verbal fluency. *Conclusion:* Hepatitis C virus infection contributes to the neuropsychological deficits observed among HIV-infected and stimulant-dependent populations.

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HIV infection can be accompanied by neurocognitive impairment consistent with frontostriatal dysfunction.[1-5] Lifestyle factors such as needle sharing and sexual contact with multiple partners have led to a relatively high prevalence of HIV infection among methamphetamine (METH) users.[6,7] Chronic or heavy exposure to METH, without comorbid HIV infection, has also been associated with neuropsychological (NP) abnormalities.[8-13] A substantial proportion of METH users, both with and without HIV infection, may also be infected with hepatitis C virus (HCV).[14-16]

There is evidence that HCV is neurotropic and may cause NP impairment even in the absence of advanced liver disease.[17] Thus, it is possible that neurocognitive dysfunction observed in individuals with HIV infection or substantial METH use may in part be a consequence of, or be augmented by, previously undetected concomitant HCV infection. In the current study, we investigated the contribution of HCV infection to the prevalence of global and domain-specific NP impairment in a convenience sample of participants with different combinations of HIV infection, METH dependence, and HCV infection as risk factors for neurocognitive deficits. We hypothesized that the prevalence of impairment would increase with the number of risk factors and that HCV seropositivity would contribute to cognitive impairment above and beyond the role of HIV serostatus and METH dependence.

Methods. *Subjects.* Subjects were 430 men and women participating in the program project on NeuroAIDS Effects of Methamphetamine at the University of California San Diego. They were recruited from substance dependence recovery programs and from the San Diego community. HIV infection was diagnosed by standard clinical antibody detection upon entry into the study. HCV serostatus was determined retrospectively by standard clinical antibody detection, and degree of liver disease was indexed by level of hepatic transaminases with clinical assays performed by standard methods. HCV+ participants were not undergoing interferon or combination interferon/ribavirin treatment at the time of their study visit. Urine testing for common recreational drugs was performed at the time of the study visit using the Rapid Drug Screen (Phamatic Inc., San Diego, CA). Lifetime history of substance use disorders, including meth dependence (METH+), was ascertained using the Structured Clinical Interview for the Diagnostic and Statistical Manual for Mental Disorders (4th ed.).[18] METH+ participants were required to meet lifetime dependence criteria, with abuse in the last 18 months.

Potential participants were excluded if they met criteria for a lifetime diagnosis of dependence on any other substance, except-

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Table *Demographic and clinical characteristics by HCV serostatus*

	HCV+, n = 83	HCV−, n = 347	*p* value*
Age, mean (SD); y	40.9 (7.3)	36.3 (9.3)	<0.0001
Education, mean (SD); y	11.3 (2.5)	12.7 (2.4)	<0.0001
Gender, n (%) male	71 (86)	268 (77)	0.08
Ethnicity, n (%) nonwhite	25 (30)	126 (36)	NS
Beck Depression Inventory	11.9 (8.9)	11.2 (9.6)	NS
Lifetime alcohol dependence, n (%)	30 (37)	58 (17)	<0.0001
Current (30 d) alcohol abuse, n (%)	2 (3)	8 (2)	NS
Lifetime average drinks/d of use, mean (SD)	6.8 (5.5)	4.9 (4.2)	0.001
METH use last 30 d, n (% of METH+)	15 (22)	25 (18)	NS
Grams of METH/y of use, mean (SD)	308.1 (320.1)	263.2 (290.1)	NS
Days abstinent, mean (SD)	131 (125)	145 (217)	NS
CD4 count, HIV+ only, mean (SD)	418.0 (232.1)	467.4 (309.8)	NS
Receiving ARV treatment, n (% of HIV+)	43 (93)	156 (95)	NS
ALT, U/L, mean (SD)	55.5 (38.0)	29.3 (24.6)	<0.0001
AST, U/L, mean (SD)	49.7 (24.8)	31.5 (18.1)	<0.0001
AST/ALT ratio, mean (SD)	1.0 (0.3)	1.3 (0.5)	<0.0001
Albumin, mean (SD); g/dL	4.0 (0.5)	4.2 (0.4)	<0.0001
Total bilirubin, mean (SD); mg/dL	0.67 (0.29)	0.69 (0.29)	NS
Platelets, mean (SD)	236.3 (141.5)	248.1 (93.6)	NS

HCV = hepatitis C virus; METH = methamphetamine; ARV = antiretroviral; ALT = alanine aminotransferase; AST = aspartate aminotransferase.

ing cannabis or alcohol because of their very high prevalence among the METH+ population. However, subjects with chronic long-term alcoholism or alcohol dependence within the last 12 months were excluded. Participants were requested to be abstinent from METH for at least 10 days prior to testing and show negative urine toxicology on the day of the assessment. In addition, subjects were excluded if they had neurologic or metabolic conditions unrelated to the risk factors of interest that might confound the interpretation of findings (e.g., psychosis, traumatic brain injury with loss of consciousness for >30 minutes). The normal control group consisted of participants who never met criteria for abuse or dependence for METH or other amphetamines and who were not regular stimulant users, in addition to meeting the general inclusion/exclusion criteria. All subjects provided written informed consent prior to participation.

Measures. Determination of impairment. Study participants underwent a comprehensive NP battery to assess functioning in the areas of learning, recall, attention/working memory, speeded information processing, verbal fluency, abstraction/problem solving, and motor ability. The Appendix lists the tests used to assess each domain of cognitive functioning. Individual test scores were standardized and combined to create global and domain-specific deficit scores in the following fashion: Raw test scores were converted to *T* scores (standard scores with a mean of 50 and SD of 10) using demographically corrected norms to account for the effects of age, education, gender, and ethnicity, as appropriate and available for each measure. A 0- to 5-point deficit rating was then assigned to the demographically corrected *T* scores for each test, as follows: $T > 39 = 0$ (no impairment), *T* 35 to 39 = 1 deficit point; *T* 30 to 34 = 2 points; *T* 25 to 29 = 3 points; *T* 20 to 24 = 4 points; $T < 20 = 5$ points. The global and domain-specific deficit scores were computed by adding the deficit points of the component test measures and dividing by the number of measures in a domain or over the whole battery for the global deficit score.

The resulting deficit scores are objective summary scores that reflect the number and severity of impaired performances throughout the test battery and give relatively less weight to test performances that are within normal limits. The deficit scores were used to classify individual subjects with respect to presence or absence of NP impairment. Global and domain deficit scores of ≥0.50 are considered impaired.[19,20] This cutoff reflects an average of at least mild impairment on at least half of the component measures.

Results. *Prevalence of HCV infection in cohort.* Because the original purpose of the parent program project concerned effects of HIV and METH, participants were not recruited with the intention to represent HCV-infected individuals. However, substantial numbers of HCV+ participants were discovered retrospectively, particularly among the METH+ groups. The prevalence of HCV infection was 37% among HIV+ METH+ participants, 28% among METH+ only, 7% among HIV+ only, and 2% among HIV− METH− subjects. The table summarizes demographic and clinical characteristics of the study participants, stratified by HCV serostatus. HCV+ subjects were slightly older, had somewhat lower level of education, were more likely to have been diagnosed with episodic alcohol dependence in the past, and had elevated indicators of liver function.

The resulting composition of the 430 participants was as follows: HCV− HIV− METH− = 90, HCV− HIV− METH+ = 83, HCV− HIV+ METH− = 105, HCV+ HIV− METH− = 2, HCV− HIV+ METH+ = 69, HCV+ HIV− METH+ = 33, HCV+ HIV+ METH− = 8, HCV+ HIV+ METH+ = 40. In terms of number of risk factors, this corresponds to 90 participants with none (i.e., normal controls), 190 subjects with one risk (HIV, or METH, or HCV), 110 with two, and 40 with all three risk factors.

Prevalence of NP impairment. With use of the number of risk factors as a grouping variable, a χ^2 test was employed to determine the significance of group differences in the proportion of global NP impairment (as determined by obtaining a global deficit score of ≥0.5). The prevalence of global NP impairment increased with the number of risk

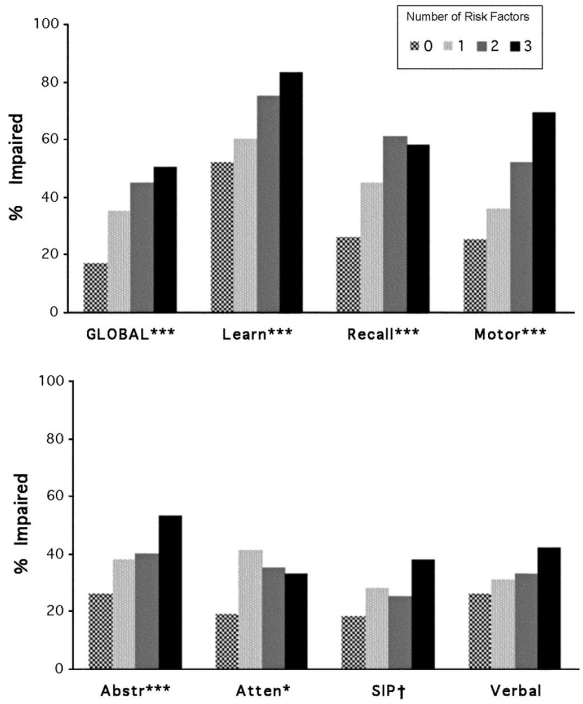

Figure. Proportion of global and domain-specific neuropsychological impairment according to number of HIV, methamphetamine, and hepatitis C virus risk factors. Somewhat elevated rates of domain-specific impairment among control subjects reflect efforts to recruit participants with comparable background characteristics. ***p < *0.001.* **p < *0.01.* *p < *0.05.* †p < *0.10. Learn = learning; Atten = attention/working memory; Abstr = abstraction/problem solving; SIP = speeded information processing.*

factors (overall $\chi^2 = 23.86$, $p < 0.0001$). Analysis of the individual ability domains showed a similar pattern, with differences in the proportion of impairment according to increasing number of risk factors in the areas of learning, motor speed and dexterity, delayed recall, and abstraction/problem solving, with a trend in speeded information processing. The proportion of impairment in attention/working memory was greater among the risk groups than in control subjects but did not increase linearly with the number of risk factors (figure).

Contribution of HCV serostatus to NP impairment. To determine whether HCV infection affected NP impairment above and beyond the contribution of HIV infection and METH dependence, we performed linear regressions predicting global and domain deficit scores. After adjusting for age, education, gender, race (white/nonwhite), history of alcohol dependence diagnosis, history of METH dependence diagnosis, and HIV serostatus, we found that HCV serostatus was a predictor of global impairment ($p < 0.02$) as well cognitive functioning in the areas of learning ($p < 0.02$), abstraction ($p < 0.02$), and motor skills ($p < 0.04$), with trends in speeded information processing ($p < 0.06$) and delayed recall ($p < 0.09$). HIV serostatus remained a predictor of the global ($p < 0.004$), learning ($p < 0.02$), delayed recall ($p < 0.03$), abstraction ($p < 0.01$), and speeded information processing ($p < 0.03$) deficit scores, with trends in attention/working memory ($p < 0.07$) and motor ability ($p < 0.08$). METH dependence remained a predictor of global ($p < 0.02$), learning ($p < 0.002$), delayed recall ($p < 0.03$), attention/working memory ($p < 0.02$), and motor ($p < 0.005$) performance, with a trend in abstraction ($p < 0.07$).

Alcohol exposure also increased with the number of risk factors, such that the average lifetime number of drinks consumed per day of use were 3.3 (SD 2.9) for control subjects, 5.1 (4.4) for those with one risk factor, 6.6 (5.2) for those with two risk factors, and 6.4 (4.9) for the three-risk group ($p < 0.0001$). When the average daily quantity was used in the regressions instead of lifetime diagnosis of alcohol dependence, the results remained essentially unaltered.

As we did not obtain liver biopsy information to determine hepatic fibrosis stage, we used available transaminase data in the form of the ratio of aspartate aminotransferase (AST) to alanine aminotransferase (ALT) as a surrogate[21] to determine the influence of liver dysfunction on NP performance among the HCV+ subjects. In correlative analyses, we found no significant relationship of the AST/ALT ratio with any of the deficit scores. Relationships between HCV viral burden and NP functioning along with other HCV-related biomarker abnormalities are reported elsewhere.[22]

Discussion. It is not known whether or how comorbid HCV infection, METH use disorders, and HIV infection may interact to worsen neurobehavioral outcomes. Observations from the current study are consistent with the hypothesis that HCV infection has an independent adverse effect on NP performance and that the effects of HCV, HIV, and METH use are additive. The results are in line with recent studies that describe neurocognitive compromise associated with HCV infection in samples with additional comorbidities. In a sample of polysubstance users, investigators found slower reaction time on a modified Stroop task among HCV+ subjects, relative to HIV+ subjects, with coinfected individuals performing worst.[23] Another recent study demonstrated worse performance on a test of abstraction and concept formation among coinfected individuals compared with those with HIV infection alone.[24] In two other studies,[25,26] NP test performance of chronic HCV patients was compared with that of patients with HCV plus comorbid conditions such as alcoholic hepatitis, HIV, hepatitis B, and other chronic liver diseases. Although deficits in attention and psychomotor speed were observed across all groups, they were most profound among HCV+ patients with comorbid conditions. Patients with chronic HCV without comorbid conditions were comparable with those with other chronic liver disease. Although a correlation was found between cognitive dysfunction and degree of hepatic fibrosis, noncirrhotic subjects had similar levels of cognitive impairment as cirrhotic subjects in many domains, suggesting that chronic liver disease, even without cirrhosis, is associated with cognitive deficits. Patients with chronic HCV were found to be impaired on more cognitive tasks than a group that had cleared HCV.[17] Impairments were seen in concentration and working memory that were independent of depression, fatigue, history of injection drug use, or symptom severity.

No consensus exists regarding HCV neuropatho-

genesis, but some theories have been postulated.[17,27,28] First, HCV may injure the brain by replicating in resident or trafficking cells. In support of this, investigators have identified that HCV can replicate in the CNS, probably in cells of macrophage lineage.[29-31] Similar to HIV, HCV might use monocyte-derived cells to enter the brain, where it could then infect resident cells. Second, infected or activated cells in the CNS may release inflammatory mediators, which can attract additional immune cells into the CNS[32] and injure neural cells. This theory is supported by the association of HCV infection with production of tumor necrosis factor- α in CSF[22] and with higher choline/creatine ratios and decreased *N*-acetylaspartate levels on MR spectroscopy.[27,33] Third, in HCV/HIV-coinfected individuals, HCV may up-regulate HIV replication in trafficking macrophages. This theory is supported by the association between HCV infection and higher HIV RNA levels in CSF.[22] Other theories of HCV neuropathogenesis are currently under investigation. For example, researchers are exploring whether HCV might injure the brain via neurotoxic HCV-encoded proteins or activation of brain endothelial cells and astrocytes.

HCV-related cognitive impairment might also result from other causes such as excitotoxic injury from hyperammonemia, which often accompanies advanced liver disease. Although we did not directly test ammonia concentrations, levels of common biochemical markers (e.g., transaminases, albumin, platelets) suggest that our study participants did not have sufficiently advanced liver disease to be at risk for hepatic encephalopathy.

Additionally, although we modeled lifetime diagnosis of alcohol dependence statistically (recent or chronic alcoholism was an exclusion criterion), the substantial prevalence of this disorder among HCV+ subjects warrants a more detailed analysis of the influence of alcohol exposure on NP functioning in this population with comorbid risks for liver dysfunction. Given its scope, this exploration is left for a separate manuscript. A preliminary analysis, however, showed that cumulative lifetime exposure to alcohol was greater in HCV+ individuals but was not correlated significantly with NP performance.

The current study adds to evidence that HCV infection has implications for brain functioning, even in the absence of advanced liver disease, and represents an early attempt at exploring the neurobehavioral consequences of possible synergy between comorbid risk factors. However, the study is limited by the lack of an HCV-monoinfected group unconfounded by METH dependence. As the original data collection was not designed to account for HCV, the available study groups were unbalanced, making it difficult to detect individual effects on brain functioning. To distinguish whether any one factor, or a specific combination, accounts for differences in the pattern or degree of NP deficits, a balanced, factorial study that includes sufficient subjects with each factor alone and in combination is required. The statistical approach employed in the current analyses is, by necessity, an imperfect attempt to tackle this question. Nevertheless, it can be argued that the participants in this study are largely representative of individuals with HCV infection, as evidenced by the degree of confounding factors reported in the extant literature and given the viral mode of transmission.

Future research directions might consider the relationship of plasma HCV burden and fibrosis indicators to NP impairment as well as effects of HCV treatment on cognitive performance. It will also be important to determine whether HCV and/or METH facilitate HIV penetration into the CNS, affect rate of neurocognitive decline, or alter neurologic response to HIV treatment. Multidisciplinary research that includes diverse sources of information (e.g., behavioral, imaging, neurobiology, and neuropathology), with proper representation of risk factors, would compose the ideal system in which to tackle the complexities of potential synergy in biologic mechanisms that may account for the increased vulnerability to neurocognitive dysfunction observed in these multirisk populations. Because hepatitis C is potentially curable, its identification and treatment are likely to result in improved neurobehavioral outcomes among individuals with HIV infection and substance use disorders.

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Appendix: Neuropsychological test battery

Domain	Tests
Estimate of premorbid functioning	WRAT-3 Reading
Verbal fluency	Letter Fluency (FAS)
	Category Fluency (Animals)
Attention/working memory	Paced Auditory Serial Addition Task
	WAIS-III Letter–Number Sequencing
Speeded information processing	WAIS-III Digit Symbol
	WAIS-III Symbol Search
	Trail Making Test A
	Stroop Task
Learning and recall	Heaton Story Memory Test
	Hopkins Verbal Learning Test–rev.
	Heaton Figure Memory Test
	Brief Visuospatial Memory Test–rev.
Abstraction/problem solving	Wisconsin Card Sorting Test
	Halstead Category Test
	Trail Making Test B
	Stroop Task Interference Ratio
Motor ability	Grooved Pegboard Test (both hands)

WRAT-3 = Wide Range Achievement Test-3; FAS = Controlled Word Association Test, letters F, A, and S; WAIS-III = Wechsler Adult Intelligence Scale-III.

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