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Absence of neurocognitive impairment in a large Chinese sample of HCV-infected injection drug users receiving methadone treatment

Saurabh Gupta^{a,e}, Jennifer E. Iudicello^a, Chuan Shi^c, Scott Letendre^a, Adam Knight^a, Jianhua Li^f, Patricia K. Riggs^a, Donald R. Franklin Jr^a, Nichole Duarte^{a,e}, Hua Jin^{a,b}, J. Hampton Atkinson^{b,a}, Xin Yu^c, Zunyou Wu^d, Igor Grant^a, Robert K. Heaton^{a,*}, and HNRC China Collaboration Group^a

^aHIV Neurobehavioral Research Program (HNRP), University of California San Diego, CA, USA

^bVA San Diego Healthcare System, San Diego, CA, USA

^cThe Institute of Mental Health at Peking University, Beijing, China

^dChina Centers for Disease Control (China CDC), Beijing, China

^eGupta Psychology & Assessment Services, USA

^fChina Yunnan Institute of Drug Abuse, Kunming, China

Abstract

Background—Prior research has demonstrated neuropsychological (NP) impairment in persons with histories of injection drug use (IDU), hepatitis C virus (HCV) infection, and methadone maintenance treatment (MMT), individually, but little is known about the NP effects of these three risk factors in combination. This issue is particularly important in China, which is addressing its highly HCV-comorbid IDU epidemic with widespread government sponsored MMT, especially in light of recent evidence suggesting that methadone may be neuroprotective in some circumstances.

Methods—We administered a comprehensive NP test battery to 195 Chinese heroin IDU individuals taking MMT (IDU+ group), the majority of whom were also HCV+ (87%; $n = 169$), and compared their NP performance to that of 198 demographically comparable, non-IDU Chinese controls (IDU− group). All participants in both groups tested negative for HIV infection, which is also a common comorbidity in the Chinese IDU population.

Results—The IDU+ group did not have an increased rate of global NP impairment, or perform significantly worse on any individual NP test measure. Within the IDU+ group, liver disease characteristics and reported details of heroin use were not significantly associated with NP performance.

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*Corresponding author at: HIV Neurobehavioral Research Program, University of California, San Diego, 220 Dickinson Street, Suite B (MC 8231), San Diego, CA 92103, USA. Tel.: +1 858 534 4044; fax: +1 619 543 1235. rheaton@ucsd.edu.

Contributors Authors Gupta, Heaton, Letendre, and Grant designed and wrote the protocol. Authors Shi, Li, Riggs, Iudicello, Knight, Jin, Atkinson, Franklin, Yu, and Wu managed the literature searches and summaries of previous related work. Authors Gupta, Iudicello, Duarte, Franklin, and Knight undertook the statistical analysis. Authors Gupta, Heaton, Jin, and Letendre oversaw analysis and interpretation of the data. All authors contributed to and approved the final manuscript.

Conflict of interest All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Author Atkinson is a consultant to Eli Lilly Pharmaceuticals. Authors Grant and Letendre are consultants to Abbott Pharmaceuticals. Author Letendre has research support paid to UCSD by Merck, Abbvie, and Glaxosmithk-line, is on the advisory board for Merck, and gives educational lectures for Biogen IDEC and Abbvie. The remaining authors declare no conflicts aside from the NIH grant support listed above.

Conclusion—Failure to detect NP impairment in IDU+ subjects with or without HCV infection was surprising, particularly considering the previously demonstrated sensitivity of our NP battery to neurocognitive disorders associated with HIV infection in China. One possible explanation, which should be explored in future research, is the potential neuroprotective effect of methadone in the context of HCV infection and/or heroin withdrawal.

Keywords

HCV; Neurocognitive impairment; China; Injection drugs

1. Introduction

The World Health Organization (WHO) estimates that approximately 150 million people worldwide are infected with the Hepatitis C virus (HCV) and over 350,000 die each year from liver diseases associated with HCV. Estimated HCV seroprevalence varies by geographic region. The highest estimated prevalence is in Egypt (15%) and Eastern European countries such as Romania (6.0%) and Ukraine (4.0%), followed by Pakistan (4.7%) and Western Europe (0.4–3.0%). While the estimated prevalence of HCV in China falls at the lower end of this range (3.2%), China's large population (1.3 billion) means that nearly 42 million people in China have been infected by HCV. Prevalence can also vary over time within regions due to social changes. In a recent study of HCV epidemiology in southwest China (Yan et al., 2012) investigators noted increases in prevalence of genotypes associated with injection drug use (IDU) since the late 1990s, which has been attributed to the proximity of southwest China to opium/heroin-producing regions in Southeast Asia.

Studies of HCV viral genetic diversity indicate that the virus can evolve independently in the brain and in the liver (Fishman et al., 2008; Maggi et al., 1999a, 1999b). HCV disease can also lead to microglial activation (Grover et al., 2012) but the extent to which this brings about a substantial neuroinflammatory response, leading to neuronal damage and cognitive impairment, has not been well established. According to the European consensus statement, neuropsychological (NP) impairment is observed in HCV, even in individuals with minimal liver disease (Schaefer et al., 2012). However, while several studies have found significant associations between HCV and NP impairment (e.g., Cherner et al., 2005; Hilsabeck et al., 2002, 2003), some of these studies included participants with potentially confounding conditions (e.g., other infections) and/or conditions associated with more advanced liver disease (e.g., hepatic encephalopathy), that are independently associated with systemic inflammation and cognitive decline (Senzolo et al., 2011), making it unclear whether and to what extent HCV itself impacts neurocognitive performance.

Injection drug use (IDU) is a significant risk factor for HCV transmission in China (Tanaka et al., 2011), and opioid drugs (e.g., heroin) are the most commonly injected worldwide. Both acute and chronic opioid use have been associated with reduced NP functioning across various domains, including attention, working memory, verbal learning and recall, executive functions (e.g., response inhibition) and psychomotor speed (Baldacchino et al., 2012; Gruber et al., 2007; Mitrovic et al., 2011; Verdejo-Garcia and Perez-Garcia, 2007). NP deficits have also been observed during opioid withdrawal (Lyvers and Yakimoff, 2003). It has been hypothesized that adverse physiological processes (e.g., immune activation and neuroinflammation) associated with opioid withdrawal may play a contributory role in both the acute and long-term CNS injury and NP impairment observed in abstinent opioid users (for a review, see Gruber et al., 2007).

Studies examining the NP effects of opioid replacement regimens used for the treatment of heroin dependence (e.g., methadone maintenance treatment, MMT) have produced mixed

results. Some, but not all, studies have found evidence for NP impairment in former heroin users on MMT relative to healthy controls or abstinent former opioid users (e.g., Darke et al., 2000; Mintzer and Stitzer, 2002; Soyka et al., 2008, 2011; Verdejo et al., 2005). Several studies (e.g., Mintzer and Stitzer, 2002; Verdejo et al., 2005) also noted that specific NP domains appear more vulnerable to the potentially adverse effects of methadone use (e.g., learning and memory) than others (e.g., attention).

No study to date has examined, in a single large sample, the NP effects of all three commonly co-occurring risk factors: HCV infection, IDU history, and MMT. The objective of this analysis was to determine the NP performance of a large sample of Chinese subjects who had a history of intravenous heroin use, were currently taking MMT, and the majority of whom were HCV seropositive. We hypothesized that both HCV seropositive IDUs and HCV seronegative IDUs would demonstrate worse NP performance relative to non-IDU controls. We also assessed whether NP performance within IDU+ participants was associated with reported amounts of prior daily heroin use, age at first use and time since last use. Similarly, for IDU+ individuals who tested positive for HCV, we assessed for possible associations between NP functioning and noninvasive measures of liver disease severity.

The current study used a comprehensive NP test battery that has been previously validated as sensitive to the cognitive effects of HIV disease and associated problems with everyday functioning in China (Cysique et al., 2007; Heaton et al., 2008). Additionally, we have reported good test–retest reliability of this test battery in China, as well as significant associations with HIV disease severity indicators, and its sensitivity to disease-related change over time and host genetic influences (Cysique et al., 2010; Schrier et al., 2012; Spector et al., 2010). The current IDU sample was unique since their MMT was carefully monitored by a government program and therefore less likely to use other drugs of abuse that could affect cognition.

2. Method

The Institutional Review Boards from the China CDC/National Center for AIDS (NCAIDS), as well as the Peking University and the University of California at San Diego (UCSD) approved the study. Participants provided informed consent for all study procedures. Participants completed standardized NP and neuromedical evaluations lasting 3.5–4 h. Compensation for these assessments was the equivalent of \$10 US.

2.1. Participants

Participants included 195 former injection drug users (IDU+) and 198 non-injection drug using controls (IDU–) residing in Gejiu, Kaiyuan, and Kunming in Yunnan Province, China (see Table 1 for proportions of individuals from each city within the IDU+ and IDU– study groups). Recruitment of IDU+ individuals was accomplished through contacts by MMT program staff, and IDU– participants were recruited through flyers and public announcements. Serologic testing included HIV quick test (OraSure Technologies, Inc, Bethlehem, PA, USA) and detection of anti-HCV IgG antibodies using an enzyme-linked immunosorbent assay (ELISA). All participants were HIV seronegative (HIV–), whereas 87% ($n = 169$) of the IDU+ group and none of the IDU– controls were HCV seropositive (HCV+). Exclusion criteria for both groups included psychotic disorders, neurological disorders (e.g., epilepsy, stroke), history of head injury with loss of consciousness of 30 min or more, and any current substance use disorders (including alcohol).

2.2. Substance use characteristics

Lifetime rates of heroin, alcohol, and other substance dependence were assessed using the World Mental Health Composite International Diagnostic Interview (WMH-CIDI; Kessler and Ustun, 2004); i.e., the Chinese version of the Composite International Diagnostic Interview (CIDI; World Health Organization, 1997). This standardized assessment of substance use disorders includes an evaluation of 15 substances: alcohol, marijuana, cocaine/crack, methamphetamine, other stimulants, heroin, other opioids, sedatives, antianxiety drugs, hallucinogens, dissociative drugs, inhalants, poppers, ecstasy, and other illicit substances. Aside from heroin, the only substance of abuse reported by the individuals in our study was alcohol. Lifetime alcohol and heroin dependence diagnoses are presented in Table 1. These lower rates of substance use disorders other than heroin are consistent with prevalence rates of illicit drug use in China, where heroin has historically been, by far, the most commonly abused illicit drug (Hao et al., 2002). Heroin use characteristics, including age at first use, days since last use, as well as reported estimates of total daily quantity and duration of peak use, were obtained from participants in the IDU+ group ($n = 195$). Total quantity of heroin use (in grams) was divided by the total duration of use (in days) to obtain a more comprehensive estimate of heroin use during peak periods.

2.3. Noninvasive estimates of liver fibrosis

Indicators of liver disease severity, including Fibrosis-4 (FIB-4) and aspartate aminotransferase-to-platelet ratio (APRI) values, were obtained for the IDU+/HCV+ subgroup ($n = 169$). FIB-4 and APRI values were calculated using published formulas (Sterling et al., 2006; Wai et al., 2003) and evaluated as continuous and discrete categories using published threshold values as indicators of severity (i.e., values greater than 1.5 and 3.25 as indicative of significant liver fibrosis for APRI and FIB-4, respectively; see Table 1). No individuals within this study were receiving HCV treatment.

2.4. Neuropsychological (NP) assessment battery

Examiners were Chinese psychiatrists and psychiatric nurses who were trained and certified by our research group in the standard administration of the NP assessment battery. The battery included 17 standardized test measures within the cognitive domains of verbal fluency, speed of information processing, learning, delayed recall, attention/working memory, executive functions, and motor speed and fine coordination (see Table 2 for a listing of specific tests). These tests are in widespread use in the US and other international contexts (e.g., Heaton et al., 2010; Hestad et al., 2012; Kanmogne et al., 2010; Joseph et al., 2013). Previous publications describe their translation and other slight modifications for use in China, as well as demonstrations of their reliability and validity in that country (Cysique et al., 2007, 2010; Heaton et al., 2008). IDU+ and IDU- groups' raw scores on the individual NP tests were compared, and associated effect sizes were reported. Raw scores were then transformed into demographically corrected T-scores, which were converted into deficit scores (see Heaton et al., 2004 for details). The latter were used to derive a Global Deficit Score (GDS); the standard GDS cutoff of 0.50 was then used to classify overall NP impairment as in prior studies (e.g., Heaton et al., 2008). This cutoff on NP test batteries has shown strong agreement with diagnostic classifications of expert clinicians, and results in false positive error rates of approximately 16% as well as good balance between sensitivity and specificity in classifying large groups of people who are normal or have well documented brain disorders (Heaton et al., 2004; Carey et al., 2004).

An adapted version of the Beck Depression Inventory-2nd edition (BDI-II; Beck et al., 1996; Zheng, 1987) was used to assess current levels of depression. The BDI-II is a 21-item, multiple-choice self-report questionnaire with total scores ranging from 0 to 63 whereby higher scores indicate greater depressive symptomatology.

2.5. Data analysis

Raw NP test scores for the two study groups were compared using ANOVA, with the alpha level set to 0.01 for Type I error control with multiple comparisons. ANOVA was also used to evaluate between group differences in BDI-II, and chi square analyses were applied to assess group differences in rates of overall NP impairment and unemployment. Cohen's *d* statistics were used to derive effect size estimates.

Correlational analyses were conducted within the IDU+ group ($n = 195$) to examine the relationship between global NP performance (i.e., GDS) and heroin use characteristics (i.e., age at first use, days since last use, quantity/duration of use), as well as length of MMT duration (for those with available data, $n = 143$). In addition, within the subsample of the IDU+ group with HCV ($n = 169$), correlational analyses were performed in order to determine the relationship between GDS and liver disease severity indices (i.e., FIB-4 and APRI).

3. Results

Demographic and socioeconomic characteristics of the study groups are summarized in Table 1. The IDU- subjects were slightly younger, more likely to be married, and had more family members, relative to IDU+ subjects ($ps < 0.05$). While the IDU+ group had slightly less income than the IDU- group ($p = 0.062$), the ratio of their total income to family size was significantly greater ($p = 0.012$). The two groups were comparable for education and gender ($ps > 0.10$). The IDU+ group reported higher levels of depressive symptoms and were much less likely to be employed than the IDU- group ($ps < 0.01$). The IDU+ group had higher proportions of lifetime alcohol dependence relative to the IDU- group ($p < 0.05$). Approximately 91% of the IDU+ group met formal criteria for lifetime heroin dependence (see Table 1).

A retrospective review of medical charts provided reliable MMT start dates for 73% ($n = 143$) of our IDU+ sample. The median duration of MMT treatment for this group was 252.0 days (interquartile range 109.0, 596.0). Of the remaining 52 individuals for whom data with regard to MMT start date was unavailable, 20 were confirmed as having dropped out of treatment. The only significant predictor of dropout was marital status, with dropouts less likely to be married relative to those who remained in treatment ($p < 0.05$). Individuals who dropped out versus those who continued did not differ in terms of other demographic (i.e., age, education, gender), socioeconomic (i.e., family income, family size), psychiatric (i.e., depression symptoms), or neurocognitive (i.e., GDS) characteristics ($ps > 0.10$).

Examination of raw (i.e., uncorrected) scores on the individual NP measures revealed that the IDU+ performed similar to the IDU- group on 15 of the 17 NP measures administered (see Table 2), and performed significantly *better* on the remaining two measures: the action (verb) fluency and Stroop color-word interference measures ($ps < 0.001$). Comparison between the IDU+ and IDU- groups on the demographically corrected GDS also revealed similar scores and proportions of impairment (17.4% and 17.2%, respectively).

Heroin use characteristics (i.e., age at first use, peak amount of daily use, and days since last use) for the IDU+ group ($n = 195$) are also summarized in Table 1. As the heroin use variables were non-normally distributed, we utilized a nonparametric approach to data analyses. No significant correlations were found between global NP performance and peak quantity/duration of daily use or days since last use ($ps > 0.10$), though a moderate association was observed between older age at first use and worse global NP performance (i.e., higher GDS; Spearman's $\sigma = 0.17$, $p = 0.023$).

Examination of the associations between global NP performance (i.e., GDS) and length of MMT treatment amongst those in the IDU+ group for whom data was available ($n = 143$) revealed a significant association between MMT treatment duration and neurocognitive impairment (i.e., proportion NP impaired). Specifically, IDU+ individuals classified as NP impaired ($n = 34$) had shorter durations of MMT treatment relative to those who were classified as NP normal ($n = 109$; $p < 0.01$). In addition, longer MMT treatment was associated with higher education, and less depressed mood ($ps < 0.05$). No significant associations were observed between MMT treatment duration and other clinical or background characteristics (e.g., age, gender, HCV status, family income and size; $ps > 0.10$).

Within the IDU+/HCV+ subgroup ($n = 169$), a substantial minority was classified with significant liver fibrosis using either APRI values (34%, $n = 57$) or FIB-r values (38%, $n = 64$). Neither of the liver fibrosis severity estimates correlated with global cognitive impairment ($ps > 0.10$).

4. Discussion

This study explored the effects of intravenous heroin use and HCV on NP functioning in a sample of Chinese individuals receiving methadone maintenance treatment (MMT), by comparing them to demographically comparable HCV seronegative Chinese individuals who had no histories of heroin use. Contrary to our expectations, we found no evidence of NP impairment attributable to these combined risk factors. The IDU+ group, most of whom had three putative risk factors for cognitive impairment (HCV infection, past injection heroin use, and current MMT) had NP test performances that were virtually indistinguishable from those of Chinese participants who had none of these risk factors. Importantly, the low prevalence of NP impairment in both study groups is consistent with that found in healthy control samples when a one standard deviation cutoff is used to classify “impairment” (e.g., Taylor and Heaton, 2001).

Additionally, historical heroin use variables (reported quantity/duration, length of abstinence from use) failed to demonstrate any association with NP performance or impairment rates. We did find a significant correlation between older age at first heroin use and worse global NP performance, though the effect size was small. Thus, it is likely that this finding reflects methodological limitations such as the use of multiple comparisons and self-report measures for the assessment of drug use history. However, it could be that individuals who begin using heroin at later ages may be more vulnerable to the NP effects of IDU and HCV, or they may benefit less from MMT. This should be explored in future research, as it could have significant treatment implications.

Although a large majority of the IDU+ participants tested positive for HCV infection, we did not find evidence to suggest that HCV itself, or markers of liver disease severity, conferred risk for NP impairment. First, no significant associations were found between overall NP impairment and estimates of liver fibrosis. Second, post hoc follow-up analyses examining differences in NP performance between the IDU- group ($n = 198$) and only those in the IDU+ group who were HCV seropositive (i.e., IDU+HCV+; $n = 169$) revealed near-identical findings to our original analyses (including IDU+ individuals with and without HCV) in terms of comparable NP performance and proportions of impairment. Moreover, within the IDU+ sample, the subgroup with HCV (IDU+HCV+) did not differ significantly from the HCV- subgroup (i.e., IDU+HCV-; $n = 26$) in terms of neurocognitive impairment status, GDS, or any of the individual neuropsychological tests listed in Table 2 (all $ps > 0.05$). Of note, the majority (i.e., >60%) of our IDU+ sample who were HCV seropositive did not have elevated markers of liver fibrosis severity. Given evidence from prior studies,

suggesting that the risk and magnitude of HCV-associated NP impairment may increase with advancing disease severity (e.g., Hilsabeck et al., 2002), future research is needed to determine whether HCV may have a more pronounced effect on NP functioning in the more advanced stages of liver disease.

One possible interpretation of the comparable NP findings in this study is that our Western NP test battery that had been translated and otherwise adapted for use in China (Cysique et al., 2007) may not be sensitive enough to detect NP impairment in these samples. However, this test battery was sensitive to relatively mild, HIV-associated neurocognitive disorders (HAND) in previous studies conducted in China (Cysique et al., 2010; Heaton et al., 2008; Schrier et al., 2012; Spector et al., 2010), and in numerous other non-Western countries including Zambia (Hestad et al., 2012), Cameroon (Kanmogne et al., 2010; Njamnshi et al., 2009), Nigeria (e.g., Royal et al., 2012), South Africa (Spies et al., 2012), India (Kamat et al., 2012), Romania (Joseph et al., 2013), and Brazil (Ellis et al., 2007), in addition to the U.S. (e.g., Heaton et al., 2010). Moreover, in the U.S., the original (English) form of the test battery has been shown sensitive to brain dysfunction associated with HCV infection and drugs of abuse (e.g., Morgan et al., 2011; Rippeth et al., 2004). Such findings argue against the possibility that the methods used here are not sufficiently sensitive to detect significant brain dysfunction that might be due to the combined risk factors observed in the Chinese IDU+ participants.

An alternate, intriguing possibility for the unexpected NP findings in this study is that MMT may protect the nervous system from the CNS injury and NP impairment that can result from opiate withdrawal. As mentioned earlier, the opioid detoxification process can produce major disturbances in the endocrine (e.g., the hypothalamic pituitary adrenal (HPA) and sympatho-adrenal-medullary (SAM) systems) and immune (e.g., dysregulation of T lymphocytes and macrophages) systems, and lead to neuroinflammation. Of particular relevance to our IDU+HCV+ sample, this process may also subsequently disrupt HCV immune responses and the impact of HCV on the liver and on the brain. Interestingly, there is some research to suggest that opioid replacement therapy may have anti-inflammatory effects, and serve a neuroprotective role. For example, Byrd and colleagues (2012) completed a post-mortem immunohistochemical analysis of brain tissue and found that the typical upregulation of pro-inflammatory molecules within HIV+ subjects was absent in those receiving MMT prior to death. Furthermore, this group also had lower levels of CD68 and CD163 expressing macrophages in brain tissue than did those without opioid dependence. These data were interpreted as evidence for an anti-inflammatory effect of MMT. The Byrd et al. study, considered alongside our results, raise the possibility that opioid substitution therapy may protect the brain from the endocrine- and immune-mediated consequences of heroin withdrawal and perhaps even HCV. Further evidence from animal models suggested that morphine may also suppress neuroinflammation (Avdoshina et al., 2010). However, more extensive research is needed before such therapeutic benefits of opiates can be inferred in humans.

Although duration of MMT treatment was significantly associated with better neurocognitive functioning, the cross sectional nature of this study does not allow for direct causal associations. It could be that MMT may have some beneficial effects on HCV disease. However, it could also be that longer MMT may reflect a higher level of functioning in general, as both higher levels of education and lower levels of depression were also predictive of longer MMT treatment durations. However, post hoc analyses also revealed that duration of MMT treatment remained a significant independent predictor of overall neurocognitive impairment even while accounting for education level and depression symptoms (i.e., BDI).

Several limitations of this study are worth noting. First, since urinalysis was not done on the day of neuropsychological testing, we cannot rule out the possibility of some unreported substance use by some of these participants. However, all participants denied such use, those who were IDU+ had daily monitoring of their MMT adherence, and examiners did not proceed with testing if there were any clinical indicators of intoxication. Also, any unreported acute use of substances is more likely to have occurred in the IDU+ group, and the absence of any worse neuropsychological functioning in that group argues against a major effect of current substance use. Second, although we examined a large, rather homogeneous sample of mostly HCV-infected IDU+ subjects participating in a government-monitored MMT program, this was not a randomized, controlled clinical trial and we cannot assume that the low frequency of NP impairment represents reversal of prior impairment. Third, we did not have any additional details regarding MMT characteristics (e.g., dosage) for our IDU+ study sample, thus we were unable to examine whether such factors may be associated with NP functioning. Given prior evidence suggesting that the severity of NP impairment associated with MMT may be dose-related (e.g., Curran et al., 2001), these factors should be carefully considered in future research. The results nonetheless are consistent with a neuroprotective effect of methadone against the deleterious effects of HCV and opioid withdrawal. Future investigations should assess HCV+/IDU+ subjects before and after initiation of opioid substitution therapy to better understand its possible benefits on the central nervous system.

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Table 1

Demographic and clinical characteristics of individuals ($n=393$) without and with injection drug use (IDU– and IDU+).

	IDU– ($n = 198$)	IDU+ ($n = 195$)	<i>p</i> -Value
Demographic characteristics			
Age (years)	34.6(6.4)	35.8 (4.9)	0.037
Education (years)	9.9(2.3)	9.8(2.5)	NS
Gender (% male)	66.2%	65.1%	NS
Socioeconomic characteristics			
Marital status (% married)	76.8%	34.4%	<0.001
Employment (% employed)	90.9%	36.6%	<0.001
Family size (total members)	3.2(1.5)	2.3(1.3)	<0.001
Total income (yuan/month)	2000.0(1000.0,3000.0)	1500.0(800.0,3000.0)	0.062
Total income/family size	600.0 (325.0,1000.0)	750.0(400.0,1250.0)	0.012
Study site			
Gejiu (%)	48.5%	22.0%	<0.001
Kaiyuan (%)	0.0%	39.5%	<0.001
Kunming (%)	51.5%	38.5%	0.009
Psychiatric and substance use characteristics			
Beck Depression Inventory-II (total score)	7.1 (7.7)	18.7(10.7)	<0.001
Heroin use characteristics			
Age at first use (years)	–	21.0(18.8, 25.0)	–
Days since last use (days)	–	90.0(19.5,365.0)	–
Total quantity/duration of use (grams/day)	–	1.0(0.5,1.0)	–
Lifetime Alcohol Dependence Diagnoses (%) ^a	2.0%	6.7%	0.022
Lifetime Heroin Dependence Diagnoses (%) ^a	0.0%	91.3%	<0.001
Medical characteristics			
Hepatitis C virus (% infected)	0.0%	86.7%	<0.001
Liver fibrosis indices			
APRI (% greater than 1.5)	–	34%	–
FIB-4 (% greater than 3.25)	–	38%	–

Note. NS = nonsignificant, $p > 0.10$; APRI = aspartate aminotransferase-to-platelet ratio; FIB-4 = fibrosis-4.

^a Diagnoses determined by Composite International Diagnostic Interview.

Table 2

Comparison of raw score neuropsychological (NP) performance and global NP impairment rates based on demographically-corrected global deficit scores for individuals ($n = 393$) without and with injection drug use (IDU- and IDU+).

Cognitive domains and neuropsychological (NP) tests	IDU- ($n = 198$)	IDU+ ($n = 195$)	<i>p</i> -Value	Cohen's <i>d</i>
Verbal fluency				
Animal fluency (total correct)	17.1 (4.9)	18.2 (4.7)	NS	–
Action fluency (total correct)	11.5(4.8)	13.6 (4.3)	<0.001	–0.46
Speed of information processing				
WAIS-III Digit Symbol (total correct)	59.6(17.1)	60.3 (14.9)	NS	–
WAIS-III Symbol Search (total correct)	33.0 (8.0)	32.3 (7.9)	NS	–
Trail Making Test Part A (completion time)	44.6(17.6)	41.7(15.6)	NS	–
Color Trails I (completion time)	42.9(13.5)	44.7(16.8)	NS	–
Learning				
HVLT-R Total Learning (3 trials)	23.7 (4.2)	24.7 (4.4)	NS	–
BVMT-R Total Learning (3 trials)	21.3(7.5)	20.2 (7.5)	NS	–
Delayed recall				
HVLT-R Delayed Recall (total correct)	8.7 (2.0)	9.0(2.1)	NS	–
BVMT-R Delayed Recall (total correct)	9.3 (2.8)	8.8 (3.0)	NS	–
Attention/working memory				
PASAT-50 (total correct)	34.5 (9.8)	32.8(11.4)	NS	–
WMS-III Spatial Span (total correct)	15.1 (3.5)	15.5 (3.0)	NS	–
Executive functions				
Color Trails II (completion time)	91.8 (27.6)	90.7 (30.1)	NS	–
Halstead Category Test (total errors)	57.7 (25.3)	56.7 (22.0)	NS	–
Stroop color-word interference test (total correct)	31.8 (9.7)	36.3(12.5)	<0.001	–0.40
Motor speed/fine coordination				
Grooved Pegboard Dominant Hand (completion time)	68.3(12.0)	67.7(13.1)	NS	–
Grooved Pegboard Non-Dominant Hand (completion time)	75.8(12.8)	75.1 (14.1)	NS	–
Global NP impairment				
Global deficit score	0.27 (0.3)	0.24 (0.3)	NS	–
Overall NP Impairment (% impaired)	17.2%	17.4%	NS	–

Note: NS = nonsignificant, $p > 0.01$ based on correction for multiple comparisons; HVLT-R = Hopkins Verbal Learning Test-Revised; BVMT-R = Brief Visual Memory Test-Revised; PASAT = Paced Auditory Serial Addition Test-50 Item Version; WMS-III = Wechsler Memory Scale-Third Edition.