The Impact of Viral Infections on Neurocognitive Functioning in the Context of Multiple Risk Factors: Associations with Health Care Utilization

by

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Abstract

Marginally housed persons experience several risk factors for neurocognitive impairment, including viral infections, psychiatric illness, and substance use. Although interventions exist, marginalized persons often obtain inadequate health services, based upon personal and structural barriers. In study one, we employed structural equation modeling to assess determinants of neurocognition (i.e., viral infections, psychiatric symptoms), predicting that any impairment would impede healthcare access. Our findings revealed that greater exposure to viral infections and more severe psychiatric symptoms were similarly associated with poorer neurocognition. Additionally, more frequent opioid use/less frequent alcohol and marijuana use was associated with better neurocognition. Only viral infections directly predicted healthcare use, an association that was positive despite the negative impact viral infections held with neurocognition.

In study two, we assessed whether spontaneous clearance of Hepatitis C (HCV) is associated with reversal of neurocognitive impairments by comparing three groups: cleared-HCV, active-HCV, and no exposure to HCV. Our findings did not confirm improved neurocognition with HCV clearance, nor did we find any differences between groups exposed to HCV versus those never exposed to the virus after controlling for the effects of Hepatitis B (HBV). Nevertheless, our findings revealed that HCV conveys adverse health in marginalized persons (i.e., HCV exposure is associated with increased rates of HIV, liver dysfunction, etc.).

Overall, these findings confirm the detrimental impact of viral infections on neurocognition in marginalized persons. Moreover, although neurocognition did not emerge as a personal barrier to accessing care in marginalized settings, structural level barriers may be operating. Specifically, our results point to a system where health care is selectively utilized and may not be targeted towards all persons, such as those experiencing elevated psychiatric symptoms.

Keywords: Viral infections; neurocognition; social marginalization; health service utilization; substance use; psychiatric illness

I dedicate my dissertation to my parents, brother, and Alan. I am exceedingly appreciative of your love, support, encouragement, and patience throughout this journey.

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Lastly, I would like to thank the study participants for their ongoing involvement in this research. I hope the results from my dissertation and the larger research team contributes to more centralized and comprehensive health care services, and ultimately an improved quality of life.

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List of Acronyms

ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
anti-HBc	Core HBV antibody test
APRI	Aminotransferase-to-Platelet-Ratio
AST	Aminotransferase
BECED	Best Estimate Clinical Evaluation and Diagnosis
CANTAB	Cambridge Neuropsychological Test Automated Battery
CCI	Composite Cognitive Index
CFI	Comparative Fit Index
CMV	Cytomegalovirus
CVA	Cerebrovascular accidents
DCC	Downtown Community Courts
DTES	Downtown Eastside
ER	Emergency Rooms/Departments
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HSU	Health Service Utilization
HSV	Herpes Simplex Virus
HVLT-R	Hopkins Verbal Learning Test-Revised
IED	Intra-Extra Dimensional
MMT	Methadone Maintenance Therapy
MRI	Magnetic Resonance Imaging
PANSS	Positive and Negative Syndrome Scale
qPCR	qualitative-Polymerase Chain Reaction
RMSEA	Root Mean Square Error of Approximation (RMSEA)
RVP	Rapid Visual Information Processing
SEM	Structural Equation Modeling
SIF	Safe-injecting facility
SRMR	Standardized Root Mean Square Residual
SRO	Single Room Occupancy

TLFB	Time-Line Follow-back
TBI	Traumatic Brain Injury

Chapter 1. General Introduction

Single-room occupancy (SRO) hotels are a form of precarious housing and are often considered the only alternative to homelessness. SROs typically consist of 8 – 12m^2 rooms. Toilet and shower facilities are often shared between 10 – 15 residents (Jones et al., 2013). SRO hotels, including those located in the Downtown Eastside (DTES) of Vancouver, British Columbia, are considered marginalized and socially disadvantaged housing, such that they fail to meet one or more criteria for "acceptable" shelter. These criteria include: 1) dwelling must be in good repair according to residents, which is unsuccessfully maintained in that many SROs are infested with pests or have fire safety concerns, 2) suitable housing includes assessment of the number of bedrooms relative to the composition of the household, which is failed in the ratio of bedrooms and tenants to toilet and showering facilities, and 3) affordable housing costs less than 30% of before-tax income, which is rarely met (Jones et al., 2013).

The HOTEL study is a prospective, 10-year longitudinal cohort examination of SRO residents living in the DTES. Past research looking into marginalized populations is insufficient, in part due to the challenges accessing these living situations in a research capacity. A goal of the HOTEL study is to characterize the individuals living in SRO hotels, in an attempt to guide effective health care delivery and reduce mortality. To describe the sample (n = 371), approximately two-thirds of study participants (66.7%) reported ever being homeless (Vila-Rodriguez et al., 2013). Substance dependence is ubiquitous (95.2%) with 61.7% reporting injection drug use. Psychosis is the most common mental illness (47.4%) and a neurological disorder is present in 45% of participants, with 28% of those having definite magnetic resonance imaging (MRI) findings. Rates of viral infections are also elevated, with Human Immunodeficiency Virus (HIV) being detected in 18.4% of the sample, and Hepatitis C Virus (HCV; antibody serology) being found in 70.3% of participants. Out of a possible 12 illnesses capturing

multimorbidity (i.e., psychosis, alcohol, stimulant, or opioid dependence, movement disorder, traumatic brain injury, seizures, cognitive impairment, brain infarction, active HIV, HCV, or Hepatitis B infection), the median number of illnesses present was three within this sample. This multimorbidity index was significantly correlated with lower role functioning scores (Vila-Rodriguez et al., 2013).

Several initiatives have been implemented in marginalized settings to reduce adverse health complications and mortality associated with some of the above noted illnesses (i.e., opioid dependence, HIV infection). For instance, since establishing a safe-injecting facility (SIF) in the DTES in September 2003, overdose rates have decreased by 35% within 500 meters of the facility (Marshall, Milloy, Wood, Montaner, & Kerr, 2011). The overall findings were interpreted to suggest that SIF are safe and effective public health interventions (Marshall et al., 2011). Further, implementation of free access to HIV care in the form of highly active antiretroviral therapies has been associated with a reduction in community viral load levels, as well as new HIV diagnosis per year in a population of people living in BC (Montaner et al., 2010). Taken together, the availability and ease of access to harm reduction programs and viral treatment options have been successful at reducing mortality due to drug overdose, and transmission of viral infections within the DTES.

Despite the programs described above, mortality rates in the HOTEL sample remain elevated. During 1269 person-years of observation, 31/371 (8%) participants died (Jones et al., 2015). The standardized mortality ratio was 8.29 over a 3.8-year follow-up compared to age- and sex-matched Canadians. For participants aged 55 years or younger, psychosis and hepatic fibrosis were associated with earlier mortality; however substance use and mood disorders were not associated with premature death. Also notable was that active HCV, but not cleared HCV, was a significant predictor of hepatic fibrosis after adjusting for alcohol dependence and age. These elevated mortality rates in our sample are contributed to by low treatment rates and poor delivery platforms, such that only 32% of those with psychosis and 0% of those with persistent HCV have received treatment. Treatment rates for HIV (57%) and opioid dependence (61%) are better, yet still far from robust (Jones et al., 2015). Overall, persons with the greatest need should obtain more care, such as individuals with psychosis having access to antipsychotic medications or those with chronic HCV being provided with

effective oral treatments. Unfortunately, financial and social disadvantage continue to be risk factors for increased morbidity and mortality in a context where healthcare is available and fundamentally the same for all Canadians.

Given the range of medical conditions, psychiatric illness, and substance use present in marginalized samples, it is reasonable to expect neurocognitive impairment as an undesirable outcome. Indeed, the few studies that have examined neurocognition in marginalized/homeless persons have identified deficits (Burra, Stergiopoulos, & Rourke, 2009; Pluck, Lee, David, Spence, & Parks, 2012; Stergiopolous et al., 2015), including the HOTEL study sample where three distinct neurocognitive profiles emerged (Gicas et al., 2014). Notably, only the work done within our HOTEL sample considered the influence of viral infections finding that the highest neurocognitive functioning group (i.e., less neurocognitive impairment) had lower rates of HIV and lower rates of overall exposure to viruses (sum of five viruses; Gicas et al., 2014) compared to the other two groups with greater neurocognitive dysfunction. As summarized in Table 1.1, and will be discussed in the following chapters, the relationship between positive viral serology and neurocognitive impairments is well established. As such, overlooking viral infections as a risk factor for neurocognitive impairment is a limitation of previous research in this area. Evidently, given the high rates of untreated viral infections present in our marginalized sample, further research is needed to clarify the link between viral infections and neurocognition.

Table 1.1. Associations Between Viruses and Neurocognition

Viral Infection	Neurocognitive Impairments	References
HIV	Fine motor speed and dexterity	Chang et al., 2002; Judd et al., 2005
	Information processing speed	Carey et al., 2004; Hart et al., 1990; Llorente et al., 1998
	Learning and memory	Carey et al., 2006; Heaton et al., 2011; Maki et al., 2009; Martin et al., 2007; Woods et al., 2005
	Executive functioning	Cattie et al., 2012; Chang et al., 2002; Devlin et al., 2012; Fujiwara et al., 2015; Giesbrecht et al., 2014; Hardy et al., 2006; Heaton et al., 2011; Hinkin et al., 1999; Iudicello et al., 2008; Martin et al., 2004; Sahakian et al., 1995
HCV	Psychomotor/information processing speed	Devlin et al., 2012; Hilsabeck, Perry, & Hassanein, 2002
	Complex and auditory attention	Hilsabeck, et al. 2002; Huckans et al., 2009
	Learning and memory	Devlin et al., 2012; Huckans et al., 2009; Karaivazoglou et al., 2007
	Executive functioning	Huckans et al., 2009; Huckans et al., 2011; Lewis, Millson, & Howdle, 2004
HSV[1]	Global intelligence	Steward, Eagan, Gonzales, & Haley, 2014
	Information processing speed	Gale et al., 2016; Tarter et al., 2014
	Learning and memory	Caparros-Lefebvre et al., 1996; Gale et al., 2016; Tarter et al., 2014
CMV	Information processing speed	Gale et al., 2016; Gow et al., 2013; Shirts et al., 2008[2]; Tarter et al., 2014
	Learning and memory	Gale et al., 2016; Gow et al., 2013; Tarter et al., 2014
	Executive functioning	Shirts et al., 2008[2]
HBV	General intellectual functioning	Severtson et al., 2012
	Information processing speed	Gale et al., 2016
	Learning and memory	Gale et al., 2016; Karaivazoglou et al., 20107
	Executive functioning	Severtson et al., 2012

Note. HIV = human immunodeficiency virus; HCV = Hepatitis C virus; HSV = herpes simplex virus; CMV = cytomegalovirus; HBV = Hepatitis B Virus; [1]Evidence suggests that HSV is associated with neurocognitive impairment in persons with established brain compromise, including schizophrenia (Dickerson et al., 2003; Schretlen et al., 2010; Watson et al., 2013) and Alzheimer's disease (Guzman-Sanchez, Valdivieso, & Burgos, 2012; Kobayashi et al., 2013; Steiner et al., 2007); [2]sample of individuals diagnosed with schizophrenia or schizoaffective disorder.

The current work is presented in two separate studies, both with the intentions of providing a detailed examination of the relationship between viral infections and neurocognition in a marginalized sample. In study one, the impact of viral infections on neurocognition is examined in the context of other risk, or health, factors for neurocognitive impairment, given the multitude of medical, psychiatric and substance

use disorders present in socially marginalized samples. Further, investigations to evaluate whether viral exposure predicts health service utilization, via reduced neurocognitive functioning, are included based on the importance of access to health care in this population. Studying the interrelatedness of multiple risk factors is imperative in this marginalized sample, as it is plausible that by examining these variables in isolation important effects may be overlooked. Subsequently, this could reduce what we ascertain about determinants of neurocognition, and subsequently health maintenance.

In study two, the focus is on examining whether neurocognitive differences exist in a group of participants with spontaneous HCV clearance relative to a group with chronic HCV infection. Given the possibility of clearance of HCV, this virus provides the opportunity to determine if clearance of a virus will result in reversible effects on neurocognitive impairment.

Chapter 2. Study 1 Introduction

Marginalized persons, including those living in urban, low-income single-room occupancy (SRO) hotels, experience numerous medical and psychosocial difficulties, including a high prevalence of substance use disorders and other psychiatric illnesses (Eyrich-Garg, Cacciola, Carise, Lynch, & McLellan, 2008; Fazel, Khosla, Doll, & Geddes, 2008; Folsom & Jeste, 2002; Koegel, Sullivan, Burnam, Morton, & Wenzel, 1999; Strehlau, Torchalla, Kathy, Schuetz, & Krausz, 2012). Further, viral infections, such as Human Immunodeficiency Virus (HIV) and Hepatitis C (HCV), are prevalent (Corneil et al., 2006; Shannon, Ishida, Lai, & Tyndall, 2006). These morbidities have been observed among those living in the Downtown Eastside (DTES) of Vancouver (BC) Canada (Jones et al., 2015; Vila-Rodriguez et al., 2013), who experience an eight-fold increase in mortality compared to age- and sex-matched adults (Jones et al., 2015).

Moreover, previous work has shown that marginalized persons face a plethora of neurocognitive deficits across multiple neurocognitive domains, including attention, processing speed, memory, and executive functioning (Burra, Stergiopoulos, & Rourke, 2009; Gicas et al., 2014; Pluck, Lee, David, Spence, & Parks, 2012; Stergiopoulos et al., 2015). The potential mechanisms underlying neurocognitive deficits likely stem to some extent from the morbidities faced by marginalized persons, including substance use (Gonzalez, Vassileva, & Scott, 2009; Rourke & Grant, 2009), psychiatric illness (Bora, Harrison, Yücel, & Pantelis, 2013; Harvey & Keefe, 2009; Langenecker, Lee, & Bieliauskas, 2009; Lepage, Bodnar, & Bowie, 2014; Nair, Palmer, Aleman, & David, 2014; Porter, Bourke, & Gallagher, 2007; Schaefer, Giangrande, Weinberger, & Dickinson, 2013) and viral infections (Cattie et al., 2012; Dawes et al., 2008; Devlin et al., 2012; Gale, Erickson, Berrett, Brown, & Hedges, 2006; Giesbrecht et al., 2014; Gow et al, 2013; Hardy, Hinkin, Levine, Castellon, & Lam, 2006; Heaton et al., 2010; Heaton et al., 2011; Huckans et al., 2009; Iudicello et al., 2008; Karaivazoglou et al., 2007; Severtson, Hedden, Martins, & Latimer, 2012;

Shirts et al., 2008; Tarter, Simanek, Dowd, & Aiello, 2014). Other risk factors for neurocognitive impairment may also be operating, including traumatic brain injury (TBI; Stergiopoulos et al., 2015) and vascular risk factors (e.g., history of stroke and/or heart disease; Patel et al., 2013).

These multimorbid risk factors are more common among high-intensity users of emergency departments (ED) and acute care hospitals (Chambers et al., 2013; Hwang et al., 2013). Marginalized persons have been shown to opt for ED visits and hospitalizations over ambulatory care (Kushel, Gupta, Gee, & Haas, 2006; Masson, Sorenson, Phibbs, & Okin, 2004; Palepu et al., 1999; Parashar et al., 2014; Reid, Vittinghoff, & Kushel, 2008). Importantly, this has implications from a health economics perspective, in that the cost of overreliance on ED visits and hospital stays is greater than standard ambulatory care (French, McGeary, Chitwood, & McCoy, 2000; Graham et al., 2016; Hwang, Weaver, Aubry, & Hoch, 2011; Palepu et al., 2001). At the structural level, even with universal healthcare where inability to pay is not an impediment to access, systems may not adequately address the needs of marginalized populations (Chambers et al., 2013; Hwang et al., 2013; Joy et al., 2008; Parashar et al., 2014). Indeed, a recent report from our group concluded that the treatment delivery platforms were suboptimal, particularly for those with psychiatric illness and HCV (Jones et al., 2015).

In marginalized persons, housing instability and poor health may hinder access to routine care and medication adherence by marginalized persons (Chambers et al., 2013; Kushel et al., 2006; Masson et al., 2004; Reid et al., 2008). Further, the tendency to utilize emergency services over ambulatory care may suggest a more disorganized lifestyle, such that attending scheduled appointments with primary care clinicians may be difficult and individuals may rely on visits to the ED for minor conditions and symptoms (Hwang et al., 2013; Palepu et al., 1999). Poor health, substance use and a more disorganized lifestyle may reflect and/or contribute to neurocognitive losses in marginalized populations, which are apt to pose significant functional barriers.

Indeed, neurocognitive impairment impedes optimal use of healthcare resources (e.g., in elderly, mildly cognitively impaired, and psychiatric populations)

whereby hospital and ED visits are favoured over ambulatory care (Binder & Robins, 1990; Callahan, Hendrie, & Tierney, 1995; Chodosh et al., 2004; Grober, Sanders, Hall, Ehrlich, & Lipton, 2012; Mackin, Delucchi, Bennett, & Areán, 2011; Walsh, Wu, Mitchell, & Berkmann, 2003). Yet the association between health service utilization (HSU) and neurocognition in marginalized populations has received limited research attention. Okonkwo and colleagues (2008) identified a significant, albeit weak (r = .13), association between increased subjective cognitive complaints and greater difficulty acquiring medical care by those with HIV. Elucidating the potential drivers of neurocognition and the extent to which any impairments impact HSU of marginalized persons may reveal critical barriers to treatment.

For this study, we analyzed data from a large sample of marginally housed persons to identify: health factors that affect neurocognition (e.g., viral infections, psychiatric symptoms); the extent to which any heath factors are directly related to HSU; and whether health factors are indirectly related to HSU via neurocognitive impairment. In accord with emergent literature, we hypothesized that viral infections would emerge as the strongest determinant of cognitive impairment relative to other factors that are either less prevalent among marginalized persons and/or less detrimental to cognition (see Byrd et al., 2011; Cysique et al., 2007; Devlin et al., 2012; Giesbrecht et al., 2014; Huckans et al., 2009; Millikin et al., 2003; Parsons et al., 2006; Patel et al., 2013). Secondly, in line with prior studies (see Masson et al., 2004; Palepu et al., 1999; Parashar et al., 2014), we predicted that co-existing viral infections would be associated with more hospitalizations, yet fewer ambulatory care visits. Thirdly, based on evidence suggesting that neurocognition is a barrier to optimal healthcare use in other populations (Binder & Robins, 1990; Callahan et al., 1995; Chodosh et al., 2004; Grober et al., 2012; Mackin et al., 2011; Walsh et al., 2003), we anticipated that neurocognition would underlie the relationship between health factors and HSU, with a particular focus on viral infections given the prevalence in this sample (e.g., 70.3% of participants had positive HCV serology; Vila-Rodriguez et al., 2013).

Chapter 3. Study 1 Methods

3.1. Participants

From November 2008 to August 2012, 371 participants were enrolled in an ongoing 10-year study of mortality and morbidity among marginally housed or homeless adults. Participants were residents from one of four SRO hotels in Vancouver's DTES (Vila-Rodriguez et al., 2013) or were recruited from the downtown community court (DCC; Jones et al., 2015). Eighty percent of the DCC sample reported living in a SRO hotel at recruitment (Jones et al., 2015). Participants were followed monthly and received small honoraria for their time. Inclusion criteria included residing in a SRO hotel or attending community court, ability to speak and comprehend the English language, and the ability to provide informed consent to participate. Ethics approval was received from the Research Ethics Boards of the University of British Columbia and Simon Fraser University. See Table 3.1 for socio-demographic information reported by participants.

Table 3.1. Study 1: Sample Characteristics

Characteristic	Value
Demographics	
Age (mean years; SD)	43.01; 9.35
Education (mean years; SD)	10.33; 2.36
Sex (% female; n)	20.1; 51
Ethnicity	
White (%; n)	59.8; 152
First Nations (%; n)	26.4; 67
Black (%; n)	3.2; 8
Latino (%; n)	0.79; 2
Other/Mixed/Unknown (%; n)	9.8; 25
Employment and Housing	
Unemployment rate (%)	86.6
Mean monthly income* (mean $; SD)	852.74; 406.21
Mean number of years on the DTES (mean years; SD)	8.23; 7.14
History of homelessness (%)	71.7

Note. n = 254; *Canadian dollars.

3.2. Measures

3.2.1. Health factors

Exposure to Viral Infections

Blood samples were collected at baseline with viral serology (i.e., antibody tests) obtained for: HIV, HCV, HBV[1], CMV, and HSV. Results were quantified dichotomously (i.e., exposed or not exposed to virus). Participants with positive HCV antibodies (i.e., HCV+) underwent HCV RNA polymerase chain reaction (qPCR) test to ascertain if the infection was currently active (i.e., positive HCV antibody and positive qPCR results).

[1] Core antibody test to reflect HBV exposure.

Within the final sample, the average number of antibody positive viral infections was 2.8 (SD = 1.2). To examine this further, 2.8% of the sample had no evidence any viral infections; 10.2% had a single viral infection; 30.3% had detection of two infections; 24.0% had three infections; 26.8% had four infections, and 5.9% of the sample had antibody positive results for the five viruses assessed.

Psychiatric Symptoms

Psychiatric symptoms were quantified using data from the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), a measure used to identify the presence and severity of psychopathology symptoms. As previously reported, we computed factor analyses on the PANSS ratings, with a 3-factor solution emerging (Giesbrecht et al., 2016). This solution was found to be a reliable (i.e., stable and invariant over a one-year period) and valid measure of psychopathology in our marginalized sample. The three factors were labeled Psychosis/Disorganized, Negative/Hostility, and Insight/Awareness. Higher scores represent greater psychiatric symptom severity. Mood and anxiety disorders and symptoms (e.g., ratings from the Beck Depression Inventory) were considered, yet not included in final analyses, based on non-significant associations (see Appendix A) between these variables and neurocognition on pre-screening.

To characterize the extent of psychiatric illness in the sample, DSM-IV-TR (American Psychiatric Association, 1994) psychiatric diagnoses were made using the Best Estimate Clinical Evaluation and Diagnosis (BECED; Endicott, 1988) with psychiatrists employing all available information to determine final diagnoses. Specifically, 8.7% of the sample met criteria for schizophrenia, 5.1% met criteria schizoaffective disorder, 5.1% met criteria for bipolar disorder, and 16.2% met criteria for a major depressive disorder. Notably, 47% of the sample met criteria for a psychosis-related disorder.

Substance Use

Frequency of substance use was determined using a drug Timeline Followback approach (TLFB; Sobell, Sobell, Klajner, Pavan, & Basian, 1986). Participants were asked how many days in the past four weeks they used alcohol,

marijuana, cocaine (power and crack), heroin, and methamphetamine. Data obtained for the current month, the month prior, and the month following the neurocognitive assessment were utilized depending on timing of the neurocognitive and TLFB assessments, and data availability[2]. The average of the days of use per month was determined for each substance, which ranged from 0 days of use to 28 days of use. Methadone maintenance therapy (MMT) for opioid dependence was also quantified, with data obtained from a TLFB record of prescribed medication. A dichotomous variable was created to differentiate no versus monthly methadone use.

Recent substance use was additionally considered, using urinalysis data collected at the time of neurocognitive assessment. For 8.30% of participants who had missing or incomplete urinalysis, self-reported substance use data 24-48 hours prior to testing was substituted, given the strong agreement between self-reported substance use (TLFB) and urinalysis in this sample (Jones et al., 2013). Acute substance use was found to have no significant associations with neurocognition (see Appendix A), and as such was not included in the final analysis.

To characterize the extent of substance use disorders in our sample, alcohol use disorder had the lowest prevalence (18% of the sample) while stimulant use disorder was highly prevalent (83% of the sample). Further, as has been described previously (Jones et al., 2015) about half of the study cohort has injected drugs though few reported sharing needles. In contrast, pipe sharing was found to be a common means of drug ingestion for crack cocaine users.

Medical and Neurological Conditions

Medical morbidity focused on vascular risk factors, given the known associations with cognitive functioning. This includes history of heart disease (e.g., myocardial infarction), diabetes, cholesterol, and cerebrovascular accidents (CVA). Of those reporting a history of heart attack or disease, 9% were currently prescribed cardiac medication. For participants who reported a history of diabetes, 64% were either currently prescribed medication or presented with average blood sugar levels in

[2] Percentage of participants with 1, 2, or 3 months of available data: 10.2, 53.9, 35.8, respectively.

the diabetic range based on blood work (i.e., 6.5% or higher of glycated hemoglobin). Cholesterol levels (mmol/L) were obtained from non-fasting blood samples collected at baseline. Diagnosis of MRI-confirmed CVA was determined by a neuroradiologist using guidelines outlined by Vernooij and colleauges (2007).

Liver functioning was assessed noninvasively using the aspartate aminotransferase-to-platelet ratio index (APRI; Wai et al., 2003), a non-invasive alternative to liver biopsy for detecting hepatic fibrosis. A continous variable was emplyed in analysis, yet for descriptive purposes, values < 0.7 indicate normal functioning, values > 2.0 suggest cirrhosis, and values between 0.7 and 2.0 suggest hepatic fibrosis (Rosen, 2011).

Specific neurological conditions were also considered. Two certified neurologists (one specializing in vascular issues and one specializing in traumatic brain injury) independently reviewed MRI scans with possible evidence of trauma (neuroimaging acquisition and processing is detailed in Gicas et al., 2017). In six cases, a second neuroradiologist confirmed the nature of the observed lesions. The presence of movement disorders (i.e., parkinsonism, dyskinesia, and akathisia) were identified by psychiatrists and/or neurologists using a score of moderate or more on the Extrapyramidal Symptom Rating Scale (Chouinard & Margolese, 2005) and the Barnes Akathisia Scale (Barnes, 1989). To reduce the number of additional variables employed, associations with neurocognition were evaluated. Of these additional neurological correlates, only dyskinesia demonstrated a significant association with neurocognition (see Appendix A), and was included in the analysis. A summary of the health factor data is presented in Table 3.2.

Table 3.2. Health Factors.

Variable	Value
Viral Infections	
HIV (% positive; n)	14.2; 36
HCV (antibody; % positive; n)	69.3; 176
HBV (core-antibody; % positive; n)	39.4; 100
CMV (% positive; n)	66.9; 170
HSV (% positive; n)	89.8; 228
Psychiatric Symptom Ratings	
F1 (mean; SD): possible range 17 - 119	38.04; 10.90
F2 (mean; SD): possible range 9 - 63	18.70; 6.84
F3 (mean; SD): possible range 2 - 14	8.89; 2.04
Substance Use (based on TLFB; range 0-28 days)	
Alcohol (mean days used/month; SD)	3.66; 6.96
Heroin (mean days used/month; SD)	5.73; 9.28
Cocaine (mean days used/month; SD)	3.41; 7.30
Methamphetamine (mean days used/month; SD)	2.44; 5.57
Marijuana (mean days used/month; SD)	8.10; 10.37
Methadone Maintenance Treatment (%; n)	33.07; 84
Medical/Neurological	
History of heart attack/disease (%; n)	8.7; 22
History of diabetes (%; n)	4.3; 11
Total Cholesterol (mean mmol/L; SD)	4.05; .99
MRI-confirmed CVA (%; n)	8.7; 22
APRI (mean; SD)[a]	.61; .72
Liver Function (% abnormal; n)	22.4; 57
Normal (%; n)	77.6; 197
Fibrosis (%; n)	17.7; 45
Cirrhosis (%; n)	4.7; 12
Dyskinesia (%; n)	7.1; 18

Note. n = 254; HIV = Human Immunodeficiency Virus; HCV = Hepatitis C Virus; HBV = Hepatitis B Virus; CMV = Cytomegalovirus; HSV = Herpes Simplex Virus; F1 = Psychosis/Disorganized; F2 = Negative Symptoms/Hostility; F3 = Insight/Awareness; SD = standard deviation; MRI = Magnetic Resonance Imaging; CVA = Cerebrovascular Accident; APRI = aspartate aminotransferase-to-platelet ratio index; [a]values have been adjusted for extreme values.

3.2.2. Outcome Variables

Neurocognitive Assessment

Neurocognitive testing was conducted at baseline. The evaluation included an acculturation questionnaire to confirm English language fluency. The test battery was administered by trained research assistants and supervised by a registered neuropsychologist. Paper and pencil tests included Stroop Color-word Test (Golden, 1978) and Hopkins Verbal Learning Test (HVLT-R; Brandt & Benedict, 2001). Also administered were selected tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996).

Four neurocognitive domains were included in the analysis: processing speed (Stroop Color reading speed); verbal memory (HVLT-R delayed recall); sustained attention/working memory (CANTAB, Rapid Visual Information Processing; RVP A′); and attentional set-shifting (CANTAB, Intra-Extra-Dimensional Set-Shift, IED; total error adjusted score). To be consistent with the other neurocognitive measures, the IED was reversed-coded so that higher scores represented better performance.

Test administrator validity ratings for all tests were reviewed to ensure only valid data were included in subsequent analyses. Reasons for exclusion included refusal to complete the entire task (early discontinuation), sensory difficulties (e.g., poor eyesight, hearing loss), excessive fatigue (falling asleep during task), poor engagement in testing, and technical complications with computerized tests.

Raw data were used for analyses; however, demographically corrected neurocognitive data (i.e., T-scores) were computed in order to in characterize the extent of impairment relative to healthy persons. For all four neurocognitive measures considered, the mean T-scores were at least one standard deviation below the mean, indicative of impairment. Most notably, verbal memory performance was nearly 2 SD below the mean of the normative sample (see Table 3.3).

Health Service Utilization

HSU was evaluated using data from a health services questionnaire administered at each monthly follow-up appointment. This self-report inventory

assesses utilization of health resources, and was modified from the Canadian Community Health Survey (Gravel & Béland, 2005) to differentiate mental health (including substance use) and physical health concerns. Based on HSU-related variables examined in samples of community older adults (70+ years of age; Walsh et al., 2003), people living with HIV (Kissinger et al., 1995; Mor, Fleishman, Dresser, & Piette, 1992), and substance users (French et al., 2000; McGeary & French, 2000), the following questions were asked: "During the last month, were you hospitalized overnight or longer for problems with your: physical health or mental health?" If "yes", how many times? And "during the last month, have you ever seen or talked to on the telephone a healthcare professional about your physical health or mental health?" The number of times the participant saw or talked to the identified professional[3] was recorded.

Consistent with previous work, longitudinal healthcare data were employed to capture patterns of health service use over time (Argintaru et al., 2013; Hwang, Chambers, & Katic, 2016; Stein, Andersen, Robertson, & Gelberg, 2012; Walsh et al., 2003). Four variables were computed: frequency of hospitalizations for physical and mental health reasons; and the number of times a participant was seen by a healthcare professional in regards to physical health and mental health. The frequency of contact with healthcare providers for each of the four variables was summed for up to 13 months and this value was divided by the number of total months of available data (M = 11.00, SD = 2.60) for each participant to represent the frequency of visits per month. For example, if a participant had 10 months of available data, the frequency of visits for each HSU variable was summed and then divided by 10. The rates of ambulatory visits and hospitalizations were comparable to the rates detected in a marginalized setting (Hwang et al., 2016). See Table 3.3 for summaries of the outcome variable data.

[3] Healthcare professionals included, psychiatrist, family doctor/general practitioner, other medical doctor such as cardiologist, gynecologist or urologist, or nurse.

Table 3.3. Outcome Variables

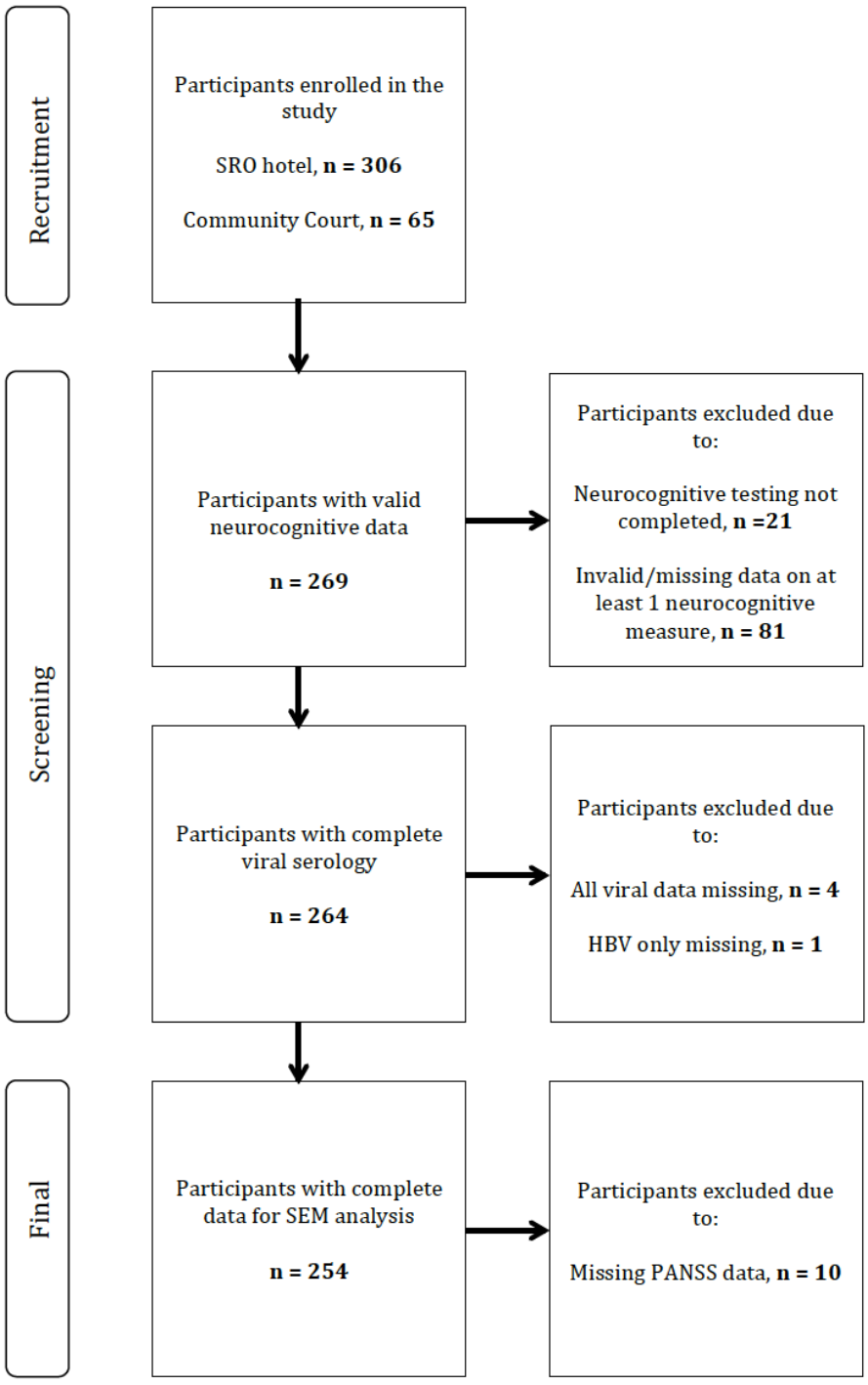
Variable	Value
Neurocognition (raw data)	
Processing Speed – Stroop Color (mean; SD)	60.70; 12.30
Verbal Memory – HVLT-R delayed (mean; SD)	6.21; 2.77
Sustained Attention – RVP A′ (mean; SD)[a]	.87; .06
Set-shifting – IED total error (mean; SD)[b]	54.13; 45.00
Neurocognition (demographically-corrected T-scores)	
Processing Speed – Stroop Color (mean; SD)	39.61; 10.10
Verbal Memory – HVLT-R delayed (mean; SD)	32.12; 11.02
Sustained Attention – RVP A′ (mean; SD)[a]	37.64; 13.90
Set-shifting – IED total error (mean; SD)[b]	37.73; 17.69
Health Service Utilization[a]	
Ambulatory Mental Health (mean visits/month; SD; range)	1.51; 1.95 (0 – 11.00)
Ambulatory Physical Health (mean visits/month; SD; range)	2.40; 4.77 (0 – 30.00)
Hospital Mental Health (mean visits/month; SD; range)	.03; .07 (0 - .35)
Hospital Physical Health (mean visits/month; SD; range)	.06; .12 (0 - .61)

Note. n = 254; SD = Standard deviation; HVLT-R = Hopkins Verbal Learning Test-Revised; RVP = Rapid Visual Information Processing; IED = Intra-Extra-Dimensional Set-Shift; [a]values have been adjusted for extreme values; [b]higher scores represent worse performance (i.e., more errors) – scores were reversed for analyses to be consistent with other neurocognitive measures (i.e., higher score equals better performance).

3.3. Data Cleaning and Assumption Checking

Only those with complete and valid neurocognitive evaluations were included in the analysis (n = 269). The Little MCAR test revealed that the data were missing at random, (χ^2 (df = 93) = 63.06, p = .993); the proportion of missing data was less than 10%. Participants with missing data on viral infections (n = 5) and PANSS data (n = 10) were excluded. The final sample included 254 participants with no missing data on any variables. No significant differences on demographic variables were found between the participants included or excluded from the study (see also Appendix B for a comparison of participants included and not included in Study 1). A flow diagram summarizing participant selection and missing data handling is shown in Figure 3.1.

Figure 3.1. Selection of Final SEM Sample.



Examination for univariate outliers revealed extreme values (>3.29 SD from the mean; Tabachnick & Fidell, 2012) on several variables (APRI, RVP A′, and the HSU variables). After confirming these data points as true values, adjustments were made according to Tabachnick and Fidell (2012) by assigning a value of one unit larger than the next most extreme non-outlier value. Thirty-four cases were statistically considered multivariate outliers through inspection of Mahalanobis distances. The most extreme cases were carefully reviewed. All cases were deemed legitimate values within this inherently variable sample[4].

Data were also assessed for normality, with many of the variables conforming to a normal distribution. However, for some variables, non-normal distributions were revealed. For APRI and IED total errors adjusted, log10 transformations were applied, which adequately normalized the distributions.

The substance use variables were positively skewed, and transformations (i.e., square root, log10, and inverse) failed to adequately normalize the distributions. Notably, similar results emerged when using transformed and untransformed data. Further, the substance use distributions likely represent the true distribution of this behaviour in this population. As such, SEM analyses were conducted on the untransformed data for ease of interpretation.

Likewise, the distributions of the HSU indicators were positively skewed. Analyses were run with transformed (i.e., log10) and untransformed data, with similar results emerging. Therefore, untransformed data was used in the final analyses to facilitate interpretation.

[4] To confirm that these 34 cases were not influencing the overall results, the final model was run excluding these participants (n = 220). The results (e.g., goodness of fit indices, relative beta rankings) were comparable to the complete sample (n = 254), and therefore the complete sample was retained for subsequent analyses.

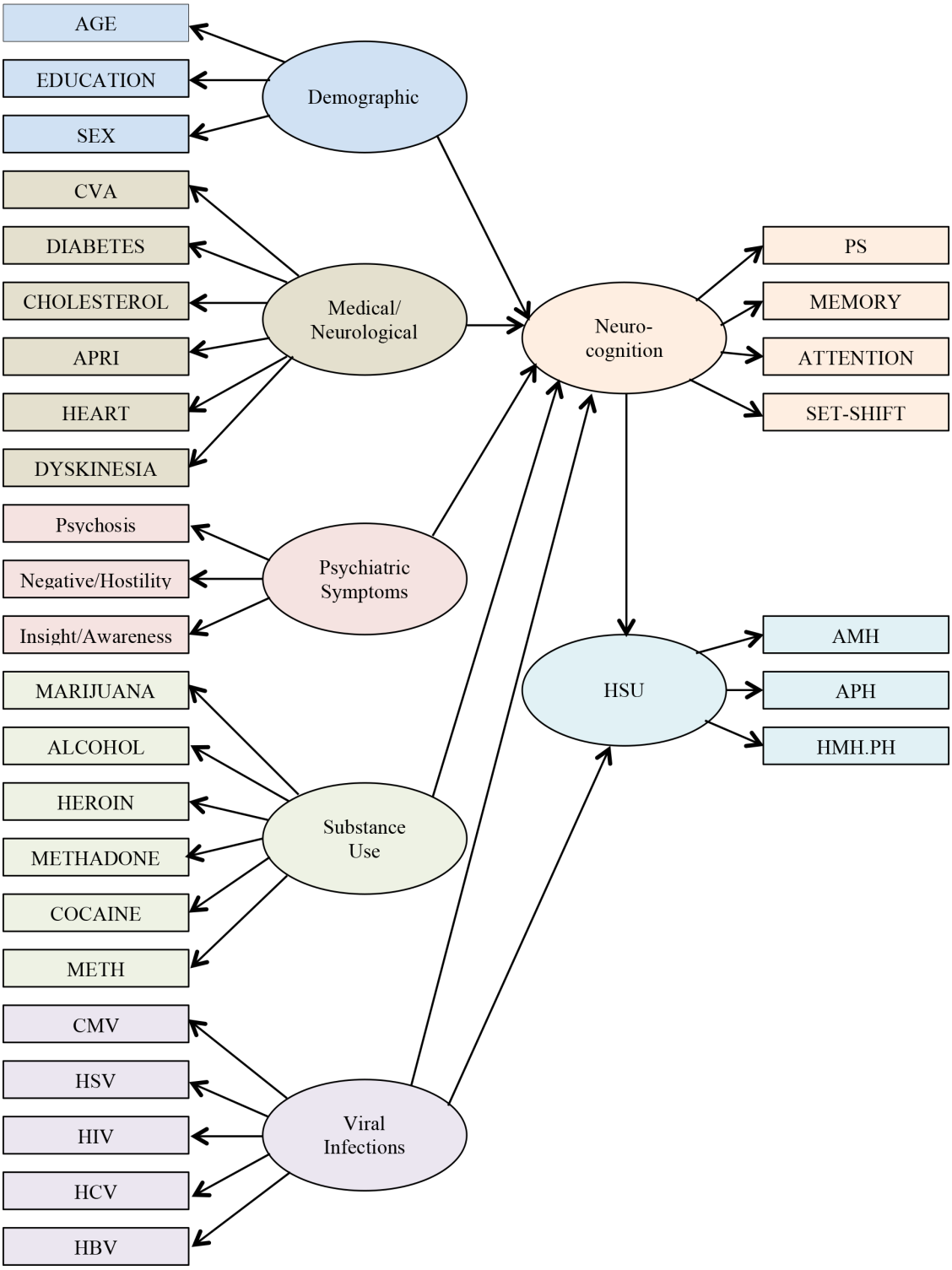
3.4. Data Analysis Plan

To test the research hypotheses, SEM was performed using maximum likelihood estimation. SEM allows for examination of multiple relationships between independent and dependent variables (observed and latent), as well as direct and indirect relationships. A further advantage of SEM over multiple regression or path analysis is the ability to estimate measurement error (Hoyle & Planter, 1995; Kline, 1998).

A baseline model was first computed in which demographic variables, medical/ neurological conditions, psychiatric symptoms, substance use, and viral infections were each assumed to predict neurocognition; in turn, neurocognition and viral infections were assumed to predict HSU. Although not hypothesized (and not illustrated as such), paths from psychiatric symptoms and substance use to HSU were also considered, and run concurrently with the path from viral infections to HSU.

Inclusion of two HSU constructs, ambulatory visits and overnight hospitalizations, each with two indicators (mental and physical health reasons), led to an unidentified model (i.e., a unique numerical solution for each of the parameters in the model was not present) possibly reflecting latent variables with only two indicators. A single HSU construct with all four indicators was also unidentified. Given that overnight hospitalizations for mental and physical health reasons were significantly correlated (rho = .22, $p < .01$) and based on low endorsements for both variables, these indicators were combined. The revised HSU construct resulted in an identified model (Figure 3.2).

Figure 3.2. Hypothesized SEM Model



Note. Hypothesized structural equation model showing the relationship between health factors, neurocognition, and HSU. Rectangles represent observed (indicator) variables while ovals represent latent variables. Error and disturbance terms have been removed for clarity. Directional pathways are illustrated with single-head arrows. CVA = cerebrovascular accident; APRI = aspartate aminotransferase-to-platelet ratio index; Heart = history of heart disease/attack; Meth = methamphetamine; CMV = cytomegalovirus; HSV = herpes simplex virus; HIV = human immunodeficiency virus; HCV = hepatitis C virus; HBV = hepatitis B virus; PS = processing speed; Set-Shift = attentional set-shifting; HSU = health service utilization; AMH = ambulatory visits – Mental Health; APH = ambulatory visits – Physical Health; HMH.PH = Overnight hospital visits for Mental and Physical Health.

Notably, including ambulatory visits with overnight hospitalizations on the same HSU construct prohibited evaluation of their divergence as anticipated. As such, follow-up correlational analyses were conducted to assess the differential relationship between service type (i.e., ambulatory vs. hospitalization) and total viral infection exposure (i.e., the number of viruses for which evidence of exposure was identified; see Gicas et al., 2014).

A subsequent SEM model was run to assess the impact of active HCV (vs. exposure) on neurocognition and/or HSU. This stems from evidence that, unlike other viral infections, HCV can be eradicated by pharmacotherapy (Fazel, Lam, Golabi, & Younossi, 2015; McNutt et al., 2012; Zhang, Bastian, & Griffin, 2015) or abate spontaneously (Forton et al., 2012; Lowry, Coughlan, McCarthy, & Crowe, 2010). A dichotomous HCV variable was computed to distinguish active and not active HCV (i.e., antibody negative, or antibody positive with negative qPCR).

Model fit between hypothesized relationships and the data was examined according to standard research and practice. Three goodness-of-fit indices were interpreted and reported. To assess whether the hypothesized model was a better fit to the data than the null model, the Comparative Fit Index (CFI), an incremental index, was used. A value of greater than .94 indicates good fit between the model and the data (Hu & Bentler, 1999). The Standardized Root Mean Square Residual (SRMR), an absolute index, was used to assess the standardized differences between observed and predicted correlations within the hypothesized model. To assess whether the hypothesized model fit the data relative to the general population from which our sample was drawn, the Root Mean Square Error of Approximation (RMSEA), a parsimony index, was estimated. For the SRMR and the RMSEA values less than

0.055 suggest good fit between the models and the data (O'Rourke & Hatcher, 2013) whereas values less than .09 suggest adequate fit (Hu & Bentler, 1999). SPSS 23.0 and AMOS 22.0 statistical software were employed for analysis.

Chapter 4. Study 1 Results

4.1. SEM Hypothesized Model

The overall goodness-of-fit between the hypothesized model and the data was marginally supported, with two indices suggesting adequate levels of fit (i.e., SRMR = .084; RMSEA = .061; .054 < RMSEA CL_{90} < .067); while the other indices were poor. Two of the five health factors (demographic and medical/neurological) were not significantly associated with neurocognition (or HSU), nor did their indicators display significant path loadings (see Appendix C for associations between neurocognition, and demographics and medical/neurological variables). These two health factors were excluded from subsequent analyses.[5] Lastly, no significant associations were found between HSU, and psychiatric symptoms and substance use, and these paths were also removed.

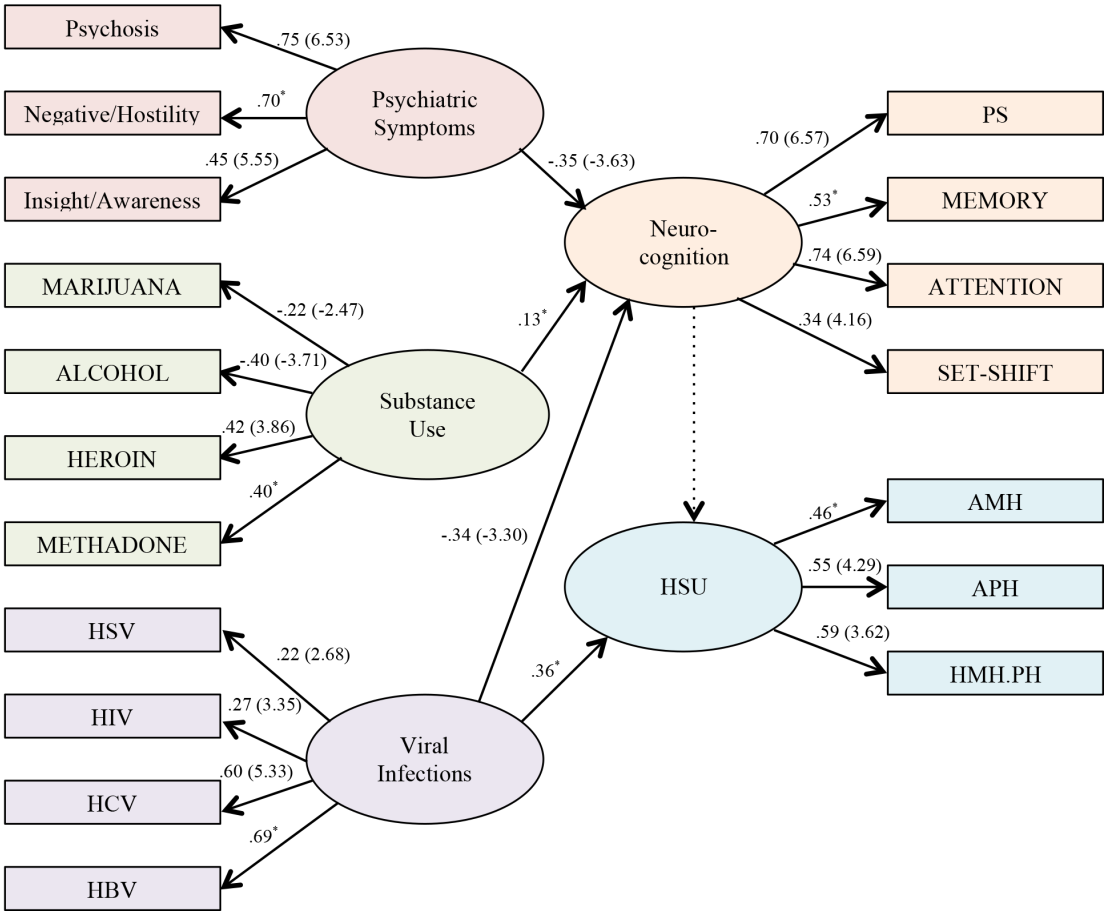
4.2. Final SEM Model – Viral Exposure

Methamphetamine and CMV were first removed from substance use and viral infections, after determining non-significant associations between these indicators and their respective latent factors. Nor did neurocognition significantly predict HSU; this path was also deleted from the model. Similarly, cocaine was removed after determining no significant loading onto the substance use latent construct. After correction for correlated error between 8 of 171 possible pairings, all goodness of fit indices were acceptable with values representing a good fit between the data and the

[5]Based on the possible influence of age and education on neurocognitive functioning, follow-up SEM was run correcting for age and education within each neurocognitive measure (Gicas et al., 2014; Giesbrecht et al., 2014). The results were similar to the model with no correction, such that age and education were not contributing to neurocognition, therefore the model was run without correction for these demographic variables.

final model, χ^2 (*df* = 125) = 136.62, *p* = .23, supporting the null hypothesis that this postulated model holds in the population. The SRMR (.055) was within acceptable limits whereas the CFI (.98) and the RMSEA (.019) were within ideal parameters. Moreover, the full 90% confidence interval for the RMSEA was within ideal limits (0 < RMSEA CL_{90} < .037). Statistical power for this model was estimated as .99 (O'Rourke & Hatcher, 2013). This final model appears in Figure 4.1.

Figure 4.1. Final SEM Model – Viral Exposure.



Note. Final structural equation model (n = 254). Values represent standardized regression weights (t-value); t-values greater than │1.96│ represent significant paths. * Path was fixed to 1 for statistical identification. HSV = herpes simplex virus; HIV = human immunodeficiency virus; HCV = hepatitis C virus (antibody); HBV = hepatitis B virus; PS = processing speed; Set-Shift = attentional set-shifting; HSU = health service utilization; AMH = ambulatory visits – Mental Health; APH = ambulatory visits – Physical Health; HMH.PH = Overnight hospital visits for Mental and Physical Health.

Viral infections (β = -.34), psychiatric symptoms (β = -.35), and substance use (β = .13) each demonstrated significant paths with neurocognition. The hypothesis that viral infections would be the strongest determinant of neurocognition was only partially supported, given that having more psychiatric symptoms was associated with poorer neurocognition to the same extent as viral infections (medium effect sizes). Substance use demonstrated a lower magnitude association with neurocognition relative to psychiatric symptoms and viral infections, and this was in the opposite direction. Notably, this was a small effect relative to the other predictors in the model, and should be interpreted tentatively.

Given the counterintuitive finding that increasing substance use was associated with better neurocognition, we examined correlations between the indicators. Only one significant association emerged, indicating that more frequent heroin use was associated with faster processing speed (Stroop Color; rho = .16, p = .01). All other correlations were non-significant (see Table 4.1) with the direction of the associations suggesting that substance use was better conceptualized as more frequent opioid use/less frequent alcohol and marijuana use.

Table 4.1. Associations Between Substance Use and Neurocognition

Neurocognition	Days of Substance Use			
Variable	**Heroin**	**MMT**	**Alcohol**	**Marijuana**
Processing Speed	.16*	.05	-.06	-.04
Delayed Memory	.10	.04	-.01	-.11#
Attention	.07	-.01	-.06	-.10
Set-Shifting	.08	-.05	-.07	-.02

Note. n = 254; MMT = methadone maintenance therapy; values represent Spearman's rho; #p < .10; *p < .05.

Viral infections, but as mentioned above not psychiatric symptoms and substance use, displayed a direct and significant association with HSU (β = .36) as greater exposure to viral infections was related to more frequent use of health services (medium effect). Counter to prediction, however, greater viral infection exposure to the four viruses that remained in the model (i.e., HIV, HCV, HBV, and HSV) was marginally associated with fewer hospitalizations (rho = -.11, p = .08). In

contrast, more viral infections were associated with more ambulatory visits, in particular for physical health reasons (rho = .19, $p < .01$) compared to mental health reasons (rho = .10, $p = .10$). Secondary analyses revealed that the above effect was possibly driven by HIV, given the significant association between HIV and ambulatory care visits for physical health reasons. See Table 4.2. As noted earlier, the path from neurocognition to HSU was not significant, therefore the hypothesis that neurocognition was directly accounting for the relationship between viral infections and HSU was not supported.

Table 4.2. Associations Between Viral Infections and HSU

Health Service Use	Viral Infections			
Variable	**HSV**	**HIV**	**HCV**	**HBV**
Ambulatory Mental Health	-.02	.02	.08	.14*
Ambulatory Physical Health	-.01	.23**	.13*	.13*
Hospitalizations	.01	-.03	-.06	-.15*

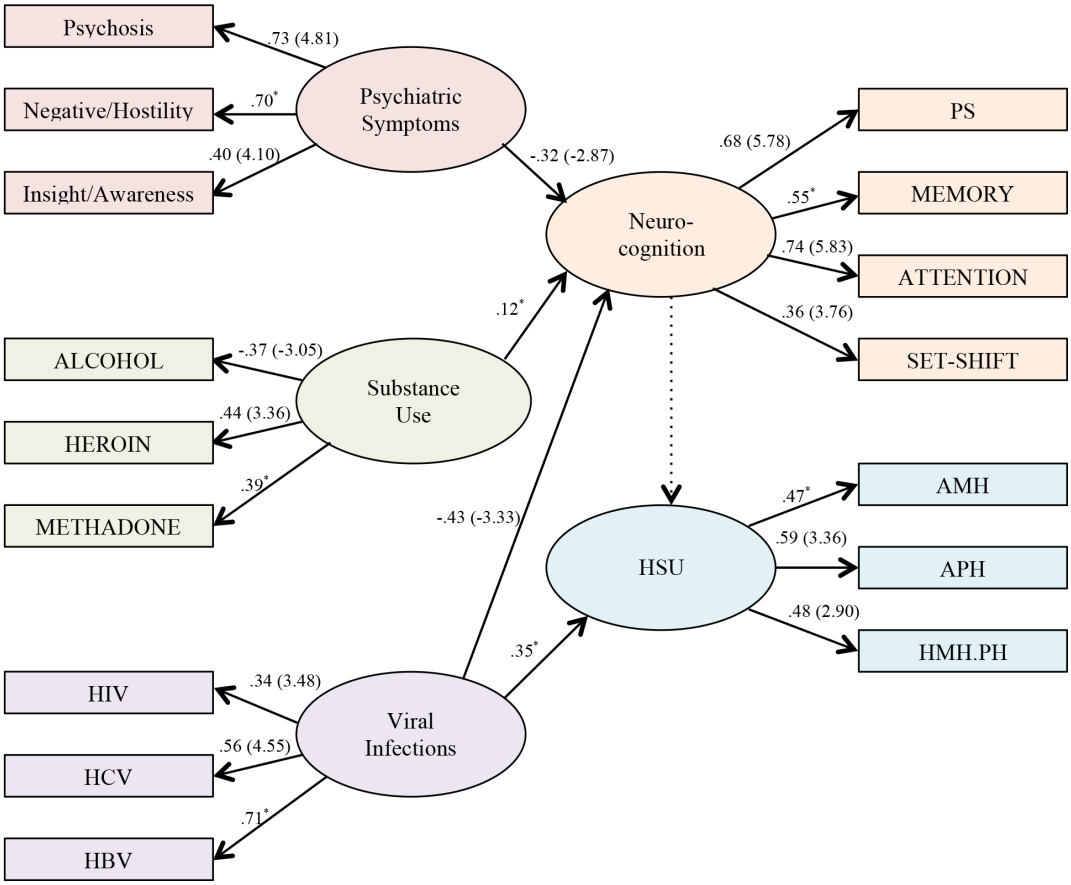
Note. Values represent Spearman's rho; HSV = Herpes Simplex Virus; HIV = Human Immunodeficiency Virus; HCV = Hepatitis C Virus; HBV = Hepatitis B Virus. *$p < .05$; **$p < .01$

The standardized regression weights between remaining indicator and latent variables in the model were significant ($p < .05$; see Figure 4.1). In terms of psychiatric symptoms as measured by the PANSS, F1 (Psychosis/Disorganized) was the strongest indicator of the psychiatric construct, followed closely by F2 (Negative Symptoms/Hostility), and lastly by F3 (Insight/Awareness). HBV was the strongest indicator of viral infections, followed by HCV, HIV, and then HSV. For neurocognition, sustained attention (RVP A′) was the strongest indicator, followed by processing speed (Stroop Color Reading Speed), verbal memory (HVLT-R delayed recall), and then attentional set-shifting (IED total errors). Overnight hospitalizations were the strongest indicator of HSU, followed closely by ambulatory visits for physical health reasons, and lastly ambulatory visits for mental health reasons. Heroin and MMT similarly loaded onto the substance use construct with positive factor loadings, with heroin identified as a slightly stronger indicator. In contrast, alcohol and marijuana negatively loaded onto the substance use construct.

4.3. Supplemental SEM Model – Active HCV

A subsequent SEM model was run to assess the impact of active HCV (vs. exposure to HCV) on neurocognition and HSU, and is hereafter referred to as the Active HCV model. The Active-HCV model (*n* = 183 due to incomplete data on the full HCV blood panel needed to determine HCV-status) with standardized regression weights appears as Figure 4.2. Generally, a solution similar to the final model emerged, except that marijuana and HSV were removed from substance use and viral infections after determining non-significant associations between these indicators and their respective latent factors. Path coefficients between the remaining indicators and latent factors were significant and followed a similar pattern as the final model. The only exception was that ambulatory visits for physical health reasons loaded most strongly on HSU. This was followed by overnight hospitalizations and ambulatory visits for mental health reasons, which were similarly associated with HSU.

Figure 4.2. Supplemental SEM Model – Active HCV



Note. Values represent standardized regression weights (t-value); t-values greater than │1.96│ represent significant paths. * Path was fixed to 1 for statistical identification. HIV = human immunodeficiency virus; HCV = hepatitis C virus (qPCR); HBV = hepatitis B virus; PS = processing speed; Set-Shift = attentional set-shifting; HSU = health service utilization; AMH = ambulatory visits – Mental Health; APH = ambulatory visits – Physical Health; HMH.PH = Overnight hospital visits for Mental and Physical Health.

After correcting for correlated error between 8 of 136 possible pairings, model fit was again assessed, χ^2 (*df* = 94) = 96.46, *p* = .41. All goodness of fit indices were acceptable, with values representing a good fit between the data and the revised model. The CFI (.99) and the RMSEA (.012) were within ideal parameters, and the 90% confidence interval for the RMSEA was also within ideal limits (0 < RMSEA CL_{90} < .042). The SRMR (.059) was acceptable.

Viral infections (β = -.43), psychiatric symptoms (β = -.32), and substance use (β = .12) demonstrated significant paths to neurocognition. Confirming our hypothesis, when considering active HCV infection over HCV exposure, viral infections were the greatest driver of neurocognitive impairment relative to the other factors in the model, a medium to large effect. As with the final model, overall substance use was positively associated with stronger neurocognition, but again, this was a small effect that should be interpreted cautiously.

Viral infections remained a direct predictor of HSU, with increasing viral infections significantly associated with greater utilization (β = .35). Again, counter to prediction, greater viral infection exposure to the three viruses that remained in the model (i.e., HIV, HCV qPCR+, HBV) was associated with fewer hospitalizations (rho = -.11, p = .13), but more ambulatory visits, in particular for physical health reasons (rho = .23, p < .01) over mental health reasons (rho = .03, p = .69). The hypothesis that viral infections and HSU would be indirectly related via neurocognition was not supported by the data.

Chapter 5. Study 1 Discussion

Marginalized persons experience numerous medical and psychosocial difficulties, and are heavy users of emergency rooms. We found that increasing exposure to viral infections and greater psychiatric symptom severity were associated with poorer neurocognition; yet, substance use (i.e., more frequent use of opioids/less frequent use of alcohol and marijuana) was associated with better neurocognition, albeit a small magnitude effect. Moreover, by including active HCV (vs. exposure to HCV), viral infections emerged with the strongest magnitude association with neurocognitive impairment. Further, viral infections were associated with more ambulatory visits but fewer hospitalizations; however, neurocognition was not underlying the relationship between viruses and HSU.

5.1. Neurocognition is not a Direct Barrier to HSU

Although inconsistent with our initial assumption, an important finding to emerge was that neurocognition was not a personal barrier to HSU in this sample, in contrast to previous work demonstrating that neurocognitive deficits impact optimal use of health services (Binder & Robins, 1990; Callahan et al., 1995; Chodosh et al., 2004; Grober et al., 2012; Mackin et al., 2011; Okonkwo et al., 2008; Walsh et al., 2003). Marginalization, including financial barriers, stigmatization, and difficulty treating comorbidities may account for this difference, in that the impediments to accessing services are so robust that even the most cognitively intact persons in our sample appear unable to effectively navigate the healthcare system. Limited knowledge around treatment availability for conditions such as substance use and/or viral infections (Edlin et al., 2005) may also be operating. For instance, within the DTES, 45% of persons surveyed (*n* = 1125; 33% infected with HCV) were unaware that there was a cure for HCV, yet greater than 80% indicated they would consider HCV treatment, if offered (Conway, Hakobyan, Vafadary, Raycraft, & Sharma, 2015).

Individuals facing barriers associated with marginalization may benefit from targeted health literacy campaigns including improved health communication to inform and influence health decisions, as has been shown to be successful in people living with HIV (Tomori et al., 2014; Vermund, Mallalieu, Lith, & Struthers, 2017).

5.2. Health Factors and HSU

Beyond personal barriers, the findings additionally contribute to research around structural barriers to HSU. We observed that persons infected with more viruses seek out ambulatory medical services without relying on inpatient care (i.e., hospitalizations). This appears at least partially driven by the positive association between HIV and ambulatory care for physical health reasons, likely reflecting the HIV treatment initiatives in place in British Columbia (Montaner et al., 2010). In contrast, psychiatric symptoms and substance use were not associated with HSU. Together, these results suggest that medical services are selectively utilized, with the possibility that persons do not actively seek out required care due to barriers at the level of the healthcare system. For instance, only 32% of participants with psychosis had received corresponding treatment at study entry (Jones et al., 2015). Moreover, despite the finding that persons with viral infections seek out care, they may not receive the most optimal treatments available. This is exemplified by the fact that, unlike the local programs implemented for HIV treatment and management (Montaner et al., 2010), none of the participants in this study are currently being treated for HCV (Jones et al., 2015), despite universal healthcare and drug coverage (i.e., PharmaCare).

Although treatment can eradicate the HCV virus, participants in our study are not being offered interventions, possibly due to various contraindications which are often considered on an individual basis (e.g., comorbid medical, psychiatric, and/or substance use, need for additional support from multidisciplinary team if co-infected with HIV, etc.; Donepudi, Paredes, Hubbard, Awad, & Sterling, 2015; Ghany, Strader, Thomas, & Seeff, 2009; Yau, Lee, Ramji, & Ko, 2015). The absence, or minimal indication, of liver fibrosis is also a barrier to treatment in BC (Yau et al., 2015), despite evidence that earlier interventions targeted to all persons with chronic HCV could reduce progression to more advance disease and limit viral transmission (e.g.,

via intravenous drug use; Myers, Shah, Burak, Cooper, & Feld, 2015). This is a substantial public health concern – in addition to contributing significantly to neurocognitive impairment, untreated HCV, via hepatic fibrosis, and psychiatric illness (e.g., psychosis) are the greatest contributors to mortality in this sample (Jones et al., 2015). Future research should continue to examine discrepancies between the needs of marginalized persons and the services they are receiving, which are unfortunately complicated by complex comorbidities in this population. Ultimately, marginalized persons may be treated most effectively by interdisciplinary teams so that treatment for viral infections, psychiatric illnesses, and substance use can each be addressed concurrently (Dimova et al., 2013; Edlin et al., 2005).

5.3. Factors Impacting Neurocognition

Our results confirm the role of multiple factors affecting neurocognition in this sample of marginalized persons. Although viral infections were strongly associated with neurocognitive impairment when considering only exposure to viruses, active HCV emerged as most integral to this association. Specifically, with active HCV infection, viral infections appeared as a remarkably strong determinant of impairment relative to psychiatric symptoms and substance use, supporting our hypothesis. Importantly, viral infections have not been routinely considered in studies examining neurocognitive functioning in unstably housed and marginalized persons (Burra et al., 2009, Pluck et al., 2012, Stergiopoulos et al., 2015). Our finding that active HCV is a significant contributor to impairment is critical given that treatments are available.

Also notable was that HBV emerged as the strongest indicator for viral infections in both the final and qPCR models. Unlike HIV and HCV, HBV has received limited attention despite evidence indicating a detrimental impact of HBV-infection on neurocognition (Severtson et al., 2012) and that HBV may be more harmful than HCV (Gale et al., 2016), or at least impacts neurocognition to the same extent (Karaivazoglou et al., 2007). It is possible that in a marginalized sample the immune system is sufficiently compromised to allow for an emergent effect of HBV on neurocognition. Additionally, in our sample, HBV may act as a proxy measure for other risk factors based on findings that HBV was positively associated with all other

viruses assessed, liver dysfunction, and heroin and cocaine use. Taken together, these findings underscore the importance of considering the impact of viruses, combined and in relation to each other, when examining neurocognition in marginalized samples.

Unexpectedly, greater frequency of substance use was significantly associated with better neurocognitive functioning, though this was a small effect relative to psychiatric symptoms and viral infections. This finding was likely driven by findings that more frequent heroin use was related to faster information processing speed. Prior meta-analytic work is consistent with this observation, proposing that opioid dependency was at least marginally and selectively associated with better neurocognitive ability (Baldacchino, Balfour, Passetti, Humphris, & Matthews, 2012). Indeed, relative to control groups, opioid dependency was associated with better cognitive flexibility (non-perseveration) yet poorer verbal working memory, cognitive impulsivity, and verbal fluency. Alternatively, it is possible that better cognitive skills are necessary to acquire heroin as opposed to alcohol and marijuana, the latter of which are arguably more readily available.

Notably, in our sample, increasing heroin use was significantly and inversely associated with less frequent alcohol (rho = -.23; $p < .01$) and marijuana use (rho = -.19; $p = .003$). By corollary, those who drink and use marijuana are less likely to use heroin. These coefficients are notable when looking at our final SEM model in which alcohol and marijuana, to a lesser degree, appear to negatively affect neurocognition whereas heroin and methadone appear to positively affect neurocognition. The 'positive' impact of heroin and methadone use may suggest that this subset of participants is less likely to drink (or use marijuana). Nevertheless, these coefficients should be interpreted tentatively as overall, substance misuse appears to have a small effect on neurocognition relative to both psychiatric symptoms and viral infections.

To further clarify the association between more frequent heroin use and faster processing speed we examined whether 1) heroin had a protective role in the context of other substances and viral infections (Gupta et al., 2014), and 2) substances differentially interact due to unique mechanisms of action (Gonzalez et al., 2004). The above explanations were not supported (see Appendix D). It is possible that multiple

variables are interacting to produce this effect, which fits with the complex multimorbidity of this sample. Further research into elucidating the findings of selectively better neurocognition with substance use is warranted.

In contrast to viral infections, psychiatric symptoms, and substance use, demographic variables were not associated with neurocognition in our model. Limited variability may have prevented detection of a sizeable effect; very few participants were under the age of 30 (9.4% of sample) or over the age of 60 (2.0% of sample), and the majority of participants (53.1%) had 10 to 12 years of education. Moreover, age and education may act as proxy variables for various factors that impact neurocognition (e.g., exposure to adverse life events, hypertension; Heaton, Ryan, & Grant, 2009), which may be captured by remaining variables in our SEM model.

Along with demographic variables, medical and neurological conditions were not associated with neurocognition, in line with previous studies indicating a limited effect of cardiovascular disease on neurocognition in the presence of HIV, CMV, and/or HSV (Strandberg et al., 2003; Thames et al., 2011). While liver dysfunction has been found to contribute to neurocognitive impairment (Karaivazoglou et al., 2007), this was not supported with our data based on non-significant correlations between abnormal liver functioning and neurocognition. Nevertheless, evidence of hepatic fibrosis may have influenced the association between risk factors with HSU, and as such future analyses into whether liver functioning was better apt to be placed on a different construct (e.g., viral infections) is warranted. Additionally, many of the medical and neurological variables were infrequently detected and/or endorsed by the participants and were often more chronic, possibly being overshadowed by more acute drivers of impairment (e.g., psychiatric symptoms, substance use).

This also underscores the importance of omnibus analyses combining a cross-section of factors affecting neurocognition and HSU in samples with comorbid psychiatric, health and substance use disorders. For instance, socio-demographic and medical and neurological factors may appear to be significant determinants of neurocognition and HSU in isolation yet these drop away when examined in conjunction with more salient factors. In other words, univariate analyses may overstate the importance of comparatively distal factors and suggest causal links

where none exist. Moreover, multivariate analyses allowed us to examine the relative importance of determinants of neurocognition and HSU.

5.4. Limitations

Despite the novel contributions of this study, limitations need to be acknowledged. The current sample presents with a multitude of medical and psychiatric symptoms, thus generalizability will be restricted to similarly multimorbid populations living in other citiies. Nevertheless, the complexity of marginalized groups should not preclude examination of the links between health factors, neurocognition and HSU, as collectively understanding these relationships could inform policy and healthcare management in persons that very much require access to appropriate and effective medical treatment (e.g., antiretrovirals, psychiatric interventions).

Notwithstanding our intentions to independently examine ambulatory visits and hospitalizations, as these constructs are assumed to capture different aspects of health care, limitations of the data (i.e., an unidentified model) precluded this analysis. To address this, follow-up correlational analyses were conducted to assess the differential impact of viral exposure on type of medical visit. Moreover, a component of HSU may have been overlooked by not evaluating ED visits, as there is often an overreliance of this form of HSU in marginalize populations. This may reflect a lack of knowledge regarding where to seek care or perceived discrimination in health care settings (Hwang et al., 2013). Future work to include ED visits is warranted.

Further, the sample size for the SEM HCV-qPCR model (n = 183) was slightly less than recommended (n > 200) for this statistical procedure (Kline, 1998). Given the consistency of this model with the final SEM model, this reduced sample was considered adequately large to gain insight into the impact that active HCV has on neurocognition. Nevertheless, these findings would likely benefit from replication with a larger sample.

Moreover, some data were obtained via self-report only without objective corroboration. Given the neurocognitive deficits, this could impact the reliability and

validity of responses. As much as possible objectively collected data was utilized, including blood work for viral infections, psychiatrist ratings for psychiatric symptoms, MRI data for CVA, and neurocognitive testing. In contrast, data surrounding select medical conditions, including history of heart disease and diabetes were based solely on self-report, which could impact the reliability of these measures. Health service use data was also collected via self-report with no corroborating evidence (e.g, hospital admittance records), although a recent study suggests that adults experiencing homelessness display accuracy in self-reported health care use, especially for ED encounters and hospitalizations (Hwang et al., 2016).

Further, given that assessing neurocognition was only one component of this comprehensive data collection, the assessment battery was designed to be brief. In doing so, select domains of neurocognition with possible signal towards HSU may have been overlooked (e.g., planning and organization). In line with this, the conclusions drawn regarding neurocognition are restricted to the aspects of neurocognition assessed (i.e., the specific tests used). Further, the reliability and validity of the inferences made from these measures will impact the statistical findings reported. That being said, the neurocognitive measures used in this study have been found to be associated with structural brain markers (Gicas et al., 2017).

Lastly, although we found that neurocognition was not a barrier to HSU when examined in relation to viral infections, psychiatric conditions and substance use disorders, it is possible that neurocognitive impairments could manifest during appointments with healthcare professionals and affect the quality of care delivered (Ganguli et al., 2006; Jones, Tabassum, Zarow, & Ala, 2015; Walsh et al., 2003). For instance, memory dysfunction could make an individual a poor historian of their most recent and pertinent medical concerns, attention difficulties may lead them to missing important health-related details, and slowed processing speed may limit ability to bring up issues in a timely fashion during often short (< 10 minute) outpatient doctor visits. These research questions should be addressed in future work.

5.5. Conclusion

To the best of our knowledge, this study represents one of the most comprehensive multivariate analyses of neurocognition and HSU in socially marginalized persons. Viral infections have received limited focus in studies examining neurocognitive deficits in unstably housed samples. The decision to include viruses was well supported, such that in the context of various health factors, viral infections were strongly associated with neurocognitive impairment. Although we found that neurocognitive impairment was not a personal barrier to HSU in this sample, future research should address the extent to which deficits in memory, attention and/or processing speed impact the ultimate quality of health intervention and the subsequent benefit. Additional personal barriers, including treatment knowledge and health literacy, should also be examined. Lastly, the healthcare needs of our cohort of marginalized persons were not adequately met, in that viral infections, but not psychiatric symptoms and substance use, were associated with health service use.

Chapter 6. Study 2 Introduction

In the context of illicit drug use and psychiatric illness, HCV infection rates are elevated in unstably housed and homeless individuals (Cheung, Hanson, Maganti, Keeffe, & Matsui, 2002; Hall, Charlebois, Hahn, Moss, & Bangsberg, 2004; Nyamathi et al., 2002). As described in Chapter 1, within our sample of SRO hotel tenants living in the DTES of Vancouver, BC 70% have positive HCV antibody tests, indicative of exposure to the virus (Vila-Rodriguez et al., 2013).

HCV primarily infects liver cells; yet travel across the blood-brain barrier with widespread distribution. Indeed, HCV has been detected in peripheral blood mononuclear cells, cerebrospinal fluid (CSF), and brain tissue (Dustin & Rice, 2007; Morgello, 2005; Weissenborn et al., 2009). Entry of HCV into the brain has been associated with neurocognitive impairment in several domains, including verbal learning and memory (Huckans et al., 2009; Karaivazoglou et al., 2007), reasoning/mental flexibility (Huckans et al., 2009, 2011), and complex attention, psychomotor/processing speed, and visuoconstructional abilities (Hilsabeck, Hassanein, Carlson, Ziegler, & Perry, 2003; Huckans et al., 2009; Thames et al., 2015). These impairments persist in the absence of liver disease (Letendre et al., 2005) and hepatic encephalopathy (Forton, Taylor-Robinson, & Thomas, 2003; Quarantini et al., 2009). Further, HCV-associated neurocognitive impairment emerges independently of HIV serostatus (Letendre et al., 2005) and substance use (Huckans et al., 2009; Letendre et al., 2005). The effects of HCV on neurocognition are particularly concerning in a sample of SRO tenants living in the DTES given the multitude of other factors that impair neurocognition (i.e., substance use, HIV and other viral infections, etc.; Gicas et al., 2014), and could result in in greater difficulties with complex everyday activities, including medication adherence (Ettenhofer et al., 2009).

Approximately 25% of individuals spontaneously clear HCV (Grebely, Raffa, Lai, Krajden, Conway, & Tyndall, 2007) and limited evidence implies the potential for reversibility of neurocognitive impairment in these persons. Cross-sectional work indicates that persons with active HCV have poorer concentration and working memory relative to persons who cleared HCV, after controlling for intravenous drug use history, depression, fatigue, and self-reported health symptom severity (Forton et al., 2002). Similarly, in a sample of woman with no history of substance use, psychiatric illness, or other medical conditions, HCV-active participants showed "memory impairment" defined by poorer delayed auditory recognition memory and overall memory scores, whereas no neurocognitive deficit was found in the spontaneously cleared HCV group (Lowry et al., 2010). In both studies, the HCV-cleared group did not significantly differ from a never-infected control group on any of the neurocognitive domains assessed.

In the context of active HCV emerging as an integral determinant of the association between viral infections and neurocognition in Study 1, Study 2 further investigates the extent of HCV-related neurocognitive impairment in a sample of marginalized persons. This work extends prior research by 1) employing a larger number of HCV-cleared and active participants, 2) including participants with viral co-infections (e.g., HCV-HIV; HCV-HBV, etc.), and 3) investigating the effects of spontaneous HCV clearance within a highly marginalized sample exposed to numerous determinants of neurocognition (i.e., viral infections, substance use, and psychiatric illness). Consistent with the contention that neurocognitive impairment may be reversed to some extent with spontaneous clearance of HCV we hypothesize that persons who have cleared HCV infection will exhibit better neurocognition relative to persons with active HCV, and that persons never infected with HCV will exhibit the strongest neurocognitive capacities compared to persons exposed to HCV.

Chapter 7. Study 2 Methods

7.1. Participants

As outlined in Chapter 3, residents (*n* = 371) of SRO hotels in Vancouver's DTES were enrolled in a 10-year longitudinal study. Participants were evaluated in monthly follow-up sessions. Inclusion criteria involved residing in a SRO hotel, ability to speak and comprehend language, and the ability to provide written consent to participate. This study was approved by the Clinical Research Ethics Board of the University of British Columbia and Simon Fraser University (SFU).

7.2. Measures

7.2.1. Blood Work and Viral Serology

Blood samples were collected at baseline assessment. Viral serology using antibody tests was obtained for HCV along with four additional viruses: HIV, HBV, CMV, and HSV. Participants with positive HCV serology underwent qPCR tests to determine if their infection was active (presence of HCV RNA). Duration of HCV infection (years) was estimated by subtracting the date of self-reported initial infection from that of neurocognitive testing.

Specific for HBV three serological tests were run: 1) core antibody (anti-HBc), 2) surface antigen test (current infection), and 3) the surface antibody test (positivity reflecting vaccination). A positive anti-HBc serological result, in the absence of a positive surface antigen and surface antibody test indicates an acute, resolved, or chronic infection, thus representing exposure to HBV by infection (Grob et al., 2000).

Liver function was assessed noninvasively via blood analysis. Specifically, aspartate aminotransferase (AST) levels were compared to platelet levels (using the local laboratory upper limits of normal, which equalled 35; Vila-Rodriguez et al., 2013) to derive APRI. APRI values greater than 0.7 suggest the presence of fibrosis and more extreme values over 2.0 are indicative of cirrhosis. For analyses, this variable was dichotomized: ≤ 0.7 (no liver dysfunction) and > 0.7 (liver dysfunction).

7.2.2. Neurocognitive Assessment

All participants included in the current study completed at least one measure of the neurocognitive battery administered (Gicas et al., 2014). Test formats included paper and pencil tests, and computerized tests from the CANTAB (Fray et al., 1996). For all participants, each neurocognitive test was screened for validity, based on ratings and comments provided by the trained research assistants administering the tests. Reasons for exclusion included: refusal to complete the entire task (early discontinuation), sensory difficulties (e.g., poor eyesight, hard of hearing), excessive fatigue (falling asleep during task), poor engagement in testing, and/or technical failure of computerized tests.

Six measures were considered from four neurocognitive tests. Processing speed and response inhibition were assessed using the Stroop-Color reading score and the Stroop Color-Word interference score, respectively (Golden, 1978). Verbal learning and memory were assessed using the HVLT-R immediate and delayed recall scores, respectively (Brant & Benedict, 2001). Sustained attention/working memory was assessed with the RVP subtest from the CANTAB, specifically looking at signal detection (A′). Attentional set-shifting was assessed using the total error adjusted score from the IED subtest of the CANTAB. Raw scores for this latter test were reversed (e.g., multiplied by -1) in order to be consistent with other tests, such that higher scores reflected better performance.

Overall neurocognitive performance was quantified using a standardized composite z-score index (Composite Cognitive Index; CCI). Details on computation of the CCI were described previously (Giesbrecht et al., 2014). Briefly, z-scores were calculated for the six measures noted above based on the mean and standard

deviation of the sample. The mean of the z-scores for each participant was taken to produce the CCI. If a participant did not complete all tasks, their CCI only included z-scores that were available. The majority of participants completed all six tasks (77.4%), 10.2% completed five of the tasks, 6.6% completed four tasks, 2.9% completed three tasks and 2.9% completed two tasks.

7.2.3. Psychiatric Disorders

The procedures for rating psychiatric disorders in this sample have been previously described (Gicas et al., 2014; Jones et al., 2013, 2015; Vila-Rodriguez et al., 2013). Briefly, diagnoses of psychiatric disorders were made by psychiatrists according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (American Psychiatric Association, 2000) through employing all available data and consensus evaluation with the Best Estimate Clinical Evaluation and Diagnosis (BECED; Endicott, 1988).

7.2.4. Substance Use Frequency

To quantify drug use at the time of neurocognitive testing the frequency of use of five different substances (alcohol, marijuana, cocaine, heroin, and methamphetamine) was determined using the TLFB method (Sobell et al., 1986). Up to 3 months of data (i.e., the month before, during, and after the baseline neurocognitive assessment) were used to create an average drug use variable encompassing the month of neurocognitive testing[6]. This average represented the number of days of reported substance use in a one-month period (range from 0 to 28 days). Intravenous drug use (IVDU) was also examined given the association with HCV infection. This data was obtained from the Maudsley Addiction Profile (Marsden et al., 1998). The number of days of self-reported injection of drugs in the past 30 days of the neurocognitive assessment was used.

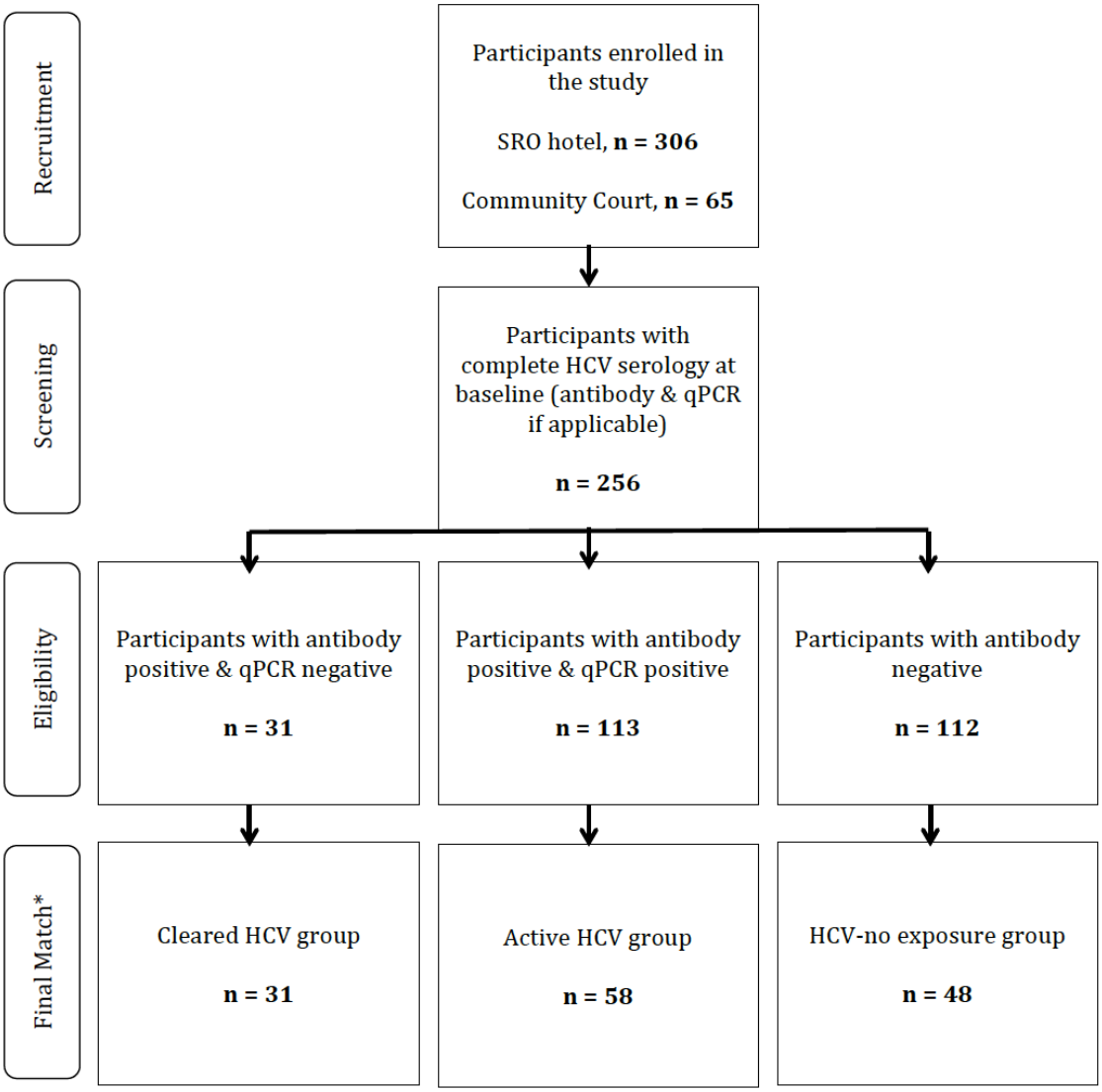
[6] If only one or two months were available this was used to create an average. Percentage of participants with 1, 2, or 3 months of available data: 14.6, 48.9, 29.9, respectively.

7.3. Data Analysis

Considering participants with the full complement of HCV data (i.e, antibody serology, and qPCR if applicable) at baseline assessment, 31 participants were positive for HCV antibodies and negative on qPCR, indicative of a *cleared HCV infection*. One hundred and thirteen participants were positive for HCV antibodies and positive for qPCR, indicating an *active HCV infection*. One hundred and twelve participants were negative for HCV antibodies, indicating *no HCV exposure*. Participants with cleared HCV comprised the smallest group, and therefore this was the reference group for matching purposes. That is, the HCV-active group and the HCV-no exposure group were matched as closely as possible to the HCV-cleared group on demographic variables (i.e., sex, age, and education). A final HCV sample was devised (n = 137 before selecting for validity of neurocognitive tests[7]), with an approximate 2:1 matching ratio of the HCV-active and HCV-no exposure groups to the HCV-cleared group. Final group sizes were: HCV-cleared n = 31; HCV-active n = 58; HCV-no exposure n = 48. A flow diagram representing group selection is shown in Figure 7.1. Sample characteristics are presented in Table 7.1. See also Appendix E for a comparison of participants included and not included in Study 2.

[7] To maximize the number of participants per HCV group for each neurocognitive comparison, validity for neurocognitive tests was selected independently for each neurocognitive measure.

Figure 7.1. Selection and Grouping of HCV Sample Participants



Note. *Prior to screening for validity of individual neurocognitive domains

Table 7.1. Study 2: Sample Characteristics

HCV status					
Characteristic	Cleared (n = 31)	Active (n = 58)	No Exposure (n = 48)	test-statistic	p-value
Demographics					
Age (mean years; SD)	44.16 (7.82)	45.57 (7.29)	43.85 (8.52)	$F = .70$	.50
Education (mean years; SD)	10.35 (2.48)	10.19 (2.15)	10.42 (2.36)	$F = .14$	.87
Sex (% Female; n)	41.9; 13	37.9; 22	27.1; 13	$\chi^2 = 2.20$	.33
Viral Infections					
HCV duration (mean years; SD)	15.36 (7.29)[a]	14.66 (7.84)[b]	n/a	$t = .36$	.72
HIV (% positive; n)	25.8; 8	29.3; 17	2.1; 1	$\chi^2 = 13.88$	.001
HBV (% positive; n)	61.3; 19	46.6; 27	8.3; 4	$\chi^2 = 27.18$	< .001
CMV (% positive; n)	74.2; 23	74.1; 43	60.4; 29	$\chi^2 = 2.76$	.25
HSV (% positive; n)	96.8; 30	96.6; 56	85.4; 41	FE = 4.87	.08
Liver Function (% abnormal; n)*	9.7; 3	36.2; 21	6.3; 3	$\chi^2 = 17.44$	< .001
Normal (%; n)	90.3; 28	63.8; 37	93.7; 45		
Fibrosis (%; n)	9.7; 3	29.3; 17	6.3; 3		
Cirrhosis (%; n)	0.0; 0	6.9; 4	0.0; 0		
Substance Use (TLFB)					
Alcohol (% using; n)	44.8; 13[c]	51.7; 30	67.4; 29[d]	$\chi^2 = 4.15$	.13
Heroin (% using; n)	51.7; 15[c]	50.0; 29	18.6; 8[d]	$\chi^2 = 12.28$	.002
Cocaine (% using; n)❖	31.0; 9[c]	56.9; 33	9.3; 4[d]	$\chi^2 = 24.77$	< .001
Methamphetamine (% using; n)	27.6; 8[c]	22.4; 13	24.4; 10[e]	$\chi^2 = .28$	.90
Marijuana (% using; n)	37.9; 11[c]	46.6; 27	60.5; 26[d]	$\chi^2 = 3.82$	.16
Intravenous Drug Use (%; n)	64.5; 20	69.0; 40	16.7; 8	$\chi^2 = 32.29$	< .001
Psychiatric Disorders					
Schizophrenia (%; n)	3.2; 1	5.2; 3	12.5; 6	FE = 2.60	.30
MDD (%; n)	16.1; 5	19.3; 11[f]	12.5; 6	$\chi^2 = .89$	.66
Psychosis-related disorder (%; n)	32.3; 10	50.0; 29	50.0; 24	$\chi^2 = 3.04$	.23
Anxiety-related disorder (%; n)	35.5; 11	29.3; 17	29.2; 14	$\chi^2 = .44$	.86

Note. SD = standard deviation; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HBV = hepatitis B virus (core antibody test; anti-HBc); CMV = cytomegalovirus; HSV = herpes simplex virus; liver function (% abnormal; n) includes fibrosis or cirrhosis; TLFB = time-line-follow back; MDD = major depressive disorder; FE = Fisher's exact test; [a]n = 22; [b]n = 47; [c]n = 29; [d]n = 43; [e]n = 41; [f]n = 57.

*Significant group difference between the HCV-cleared and HCV-active; $\chi^2 = 7.22$, $p = .01$.

❖Significant group difference between the HCV-cleared and HCV-active; $\chi^2 = 5.18$, $p = .02$.

To assess whether the three groups were matched on demographic and clinical variables, analysis of variance (ANOVA) and chi-square procedures were employed for continuous and categorical variables, respectively. The Fisher's exact test was used when the expected frequency for one or more cells was five or less. To statistically evaluate hypothesis one, that the HCV-cleared group would perform better cognitively than the active group, independent *t*-tests were utilized. To address the second hypothesis participants from the HCV-cleared and active groups were combined into a single group (HCV-exposed) and compared to the HCV-no exposure group using independent *t*-tests.[8]

7.3.1. Managing Confounding Factors

To manage potential confounds between HCV groups, the associations between comorbid conditions that differed between the groups (i.e., covariates) and neurocognitive measures (i.e., dependent variables) were screened using point biserial correlational analyses. Significant relationships (i.e., $p \leq .05$) to emerge between covariates and dependent variables were subsequently analyzed using analysis of covariance (ANCOVA) procedures to partial out variance associated with the identified confounds.

7.3.2. Data Cleaning

Data was assessed for normality and outliers as outlined by Tabachnick and Fidell (2012). The distributions for the five substance use variables and intravenous drug use were positively skewed and transformations (e.g., square root, log10, and inverse) failed to adequately correct for this. Therefore variables were dichotomized into "no use" or "at least one day of reported use". Three participants had scores on

[8] The three groups were initially compared simultaneously using analysis of variance, however, it emerged that the HCV-cleared and active groups were well-matched and better suited to be combined into a single group for comparisons to the HCV-no exposure group, which differed significantly on several clinical measures (detailed in Section 8.1).

the measure of sustained attention/working memory (RVP A′) that were considered outliers according to the 3.29 standard deviation cut-off described by Tabachnick and Fidell (2012). After confirming the validity of these scores, appropriate adjustments were made. A log10 transformation was applied to the measure of attentional set-shifting (IED total error adjusted), adequately correcting a significant positive skew. ANOVA assumptions of normal distribution of dependent variables, homogeneity of the variance (based on Levene's test), and independence of observations were met. The additional assumption for ANCOVA (i.e., homogeneity of the regression slopes) was also met for applicable analyses.

Power analysis was computed using G*Power (Faul, Erdfelder, Buchner, & Lang, 2009). Adequate sample size was achieved to detect a medium to large effect (i.e., $d = 0.7$) in the HCV-cleared vs. HCV-active comparisons, and a medium effect ($d = 0.5$) in the HCV-exposed vs. HCV-no exposure comparisons, using the smallest possible samples (i.e., analyses involving the CCI neurocognitive outcome measure), with $\alpha = .05$, and power $(1 - \beta) = 0.80$.

Chapter 8. Study 2 Results

8.1. Group Comparisons and Identification of Confounds

The HCV-cleared and active groups were well-matched across viral infections, psychiatric disorders, and substance use (with the exception of cocaine use, which was endorsed significantly more in the HCV-active group, see Table 7.1 note). The only other group difference to emerge was on rates of liver dysfunction (i.e., indications of fibrosis or cirrhosis), with approximately 36% of the active group displaying liver dysfunction compared to 10% of the cleared group. In contrast, several significant differences were identified between the HCV-exposed and HCV-no exposure groups, such that the HCV-exposed group had higher rates of HIV (28.1% vs. 2.1%), HBV (51.7% vs. 8.3%), HSV (96.6% vs. 85.4%), liver dysfunction (27.0% vs. 6.3%), cocaine (48.3% vs. 9.3%) and heroin use (50.6% vs. 18.6%), and IVDU in the past 30 days (67.4% vs. 16.7%).

8.2. HCV-cleared versus HCV-active

The hypothesis that the HCV-cleared group would exhibit better neurocognition compared to the HCV-active group was not statistically supported. Specifically, no significant differences emerged between groups on processing speed, response inhibition, verbal learning and memory, set-shifting, and overall cognition (Table 8.1). The HCV-active group showed better sustained attention (RVP A′) compared to the HCV-cleared group, a moderate effect that emerged as significant after removing persons with liver dysfunction ($t_{(53)}$ = -2.58; p = .013; Cohen's d = -

.44)[9]. Nevertheless, Bonferroni correction for multiple comparisons (α = .05/7 = .007) would render all comparisons non-significant.

Table 8.1. Neurocognitive Comparison of HCV-Cleared and -Active Groups

	HCV-Cleared			HCV-Active					
Cognitive Domain	M	SD	N	M	SD	N	*t*	*p*	E.S.
Processing Speed	59.36	12.37	28	59.93	14.15	57	-.18	.86	-.04
Response Inhibition	35.57	10.21	28	35.35	11.39	57	.09	.93	.02
Verbal Learning	17.48	4.72	27	17.96	5.30	55	-.40	.69	-.09
Verbal Memory	5.85	2.30	27	5.40	2.54	55	.78	.44	.18
Sustained Attention[a]	.84	.08	24	.86	.06	53	-1.57	.13	-.30
Set-shifting[b, c]	62.91	55.79	23	64.77	53.12	53	.04	.97	-.03
CCI	-.14	.68	21	-.05	.74	47	-.48	.63	-.13

Note. HCV = hepatitis C virus; M = mean; SD = standard deviation; E.S. = effect size (Hedges' *g*); CCI = cognitive composite index; [a]equal variances not assumed based on Levene's test for equality of variances (t-statistic reflects this); [b]higher score (more errors) represents worse performance; [c] presented data represents untransformed data, though independent t-test analyses were run on log10 transformed data.

Follow-up analyses revealed that the HCV-active group had a significantly greater probability of a hit (*M* = .55, *SD* = .22; $t_{(53)}$ = -2.26; *p* = .03) on sustained attention compared to the HCV-cleared group (*M* = .42, *SD* = .18). This score takes into account how often participants respond correctly based on the ratio of hits to misses (hits/(hits + misses)). Taken together with the signal detection (i.e., RVP A′) results noted above, these findings indicate that persons with active HCV are better at sustaining attention when working memory is required compared to persons with cleared HCV, such that they have stronger and more accurate signal detection of a target sequence[10].

[9] Given that liver dysfunction emerged as a confound between the HCV-cleared and active groups, and since only three HCV-cleared participants had evidence of liver dysfunction (compared to 21 HCV-active participants) participants with liver dysfunction were excluded and the independent *t*-test was re-run.

[10] No other group differences emerged on the remaining RVP measures, including response latency or probability of false alarms (i.e., subject responding incorrectly = (false alarms/(false alarms + correct rejections)).

Along with liver dysfunction, cocaine use at the time of neurocognitive testing was identified as a potential confound between HCV-cleared and active groups. Screening conducted within the HCV-exposed sample revealed that endorsement of cocaine use was not significantly (p > .10) associated with any of the neurocognitive measures (Spearman's *rho* ranged from -0.19 to 0.05). Therefore, no follow-up ANCOVAs were indicated.

8.3. HCV-exposed versus HCV-no exposure

The hypothesis that the HCV-no exposure group would show stronger neurocognitive performance relative to the HCV-exposed group was supported on select neurocognitive measures. Specifically, significantly better sustained attention ($t_{(118)}$ = 2.11, p = .04) was found in participants with no HCV exposure compared to the HCV-exposed group (Table 8.2). Marginally better verbal learning (HVLT immediate; $t_{(124)}$ = 1.88, p = .06) and verbal memory (HVLT delay; $t_{(124)}$ = 1.95, p = .06) was also found in the HCV-no exposure group. Again, these results should be interpreted tentatively, given that multiple comparisons were made.

Table 8.2. Neurocognitive Comparison of HCV-Exposed and HCV-No Exposure Groups

	HCV-exposed			HCV-no exposure					
Cognitive Domain	M	SD	N	M	SD	N	*t*	*p*	E.S.
Processing Speed	59.74	13.52	85	59.19	14.08	47	-.22	.83	-.04
Response Inhibition	35.42	10.95	85	33.19	10.32	47	-1.14	.26	-.21
Verbal Learning	17.80	5.09	82	19.70	5.96	44	1.88	.06	.35
Verbal Memory[a]	5.55	2.46	82	6.61	3.14	44	1.95	.06	.39
Sustained Attention	.85	.07	77	.88	.06	43	2.11	.04	.45
Set-shifting[b, c]	64.21	53.57	76	56.33	39.36	43	.02	.99	.16
CCI	-.08	.72	68	.12	.72	38	1.34	.18	.27

Note. HCV = hepatitis C virus; M = mean; SD = standard deviation; E.S. = effect size (Hedges' *g*); CCI = cognitive composite index; [a]equal variances not assumed based on Levene's test for equality of variances (t-statistic reflects this); [b]higher score (more errors) represents worse performance; [c] presented data represents untransformed data, though independent t-test analyses were run on log10 transformed data.

The impact of confounds was considered next. The presence of positive anti-HBc[11] was identified as a confound for many of the neurocognitive measures assessed, in that it was significantly associated with poorer performance on all neurocognitive measures, except for processing speed and response inhibition (Appendix F). Given that the HCV-exposed group had a significantly higher proportion of anti-HBc compared to the HCV-no exposure group, the independent *t*-tests comparing these groups were re-run excluding 4 HCV-no exposure and 46 HCV-exposed participants that were also anti-HBc positive. No significant group differences on the neurocognitive measures, including sustained attention, remained after excluding anti-HBc positive participants (Appendix G), suggesting that infection with HBV may be underlying the effect between sustained attention and HCV exposure.

A follow-up linear regression analysis (with anti-HBc participants included) was run to assess whether anti-HBc was mediating the relationship between HCV status and sustained attention, after confirming significant point biserial correlations between HCV and sustained attention (r = -.19, p = .04), HCV and anti-HBc (r = .45, p < .001), and anti-HBc and sustained attention (r = -.26, p < .01). On the first block, anti-Hbc status explained 5.5% of the variance in sustained attention ($F_{(1, 118)}$ = 6.84, p = .01). HCV status was entered on block two, and did not explain any significant variance in sustained attention (0.90%), over and above that explained by anti-HBc, ($F_{(1, 117)}$ = 1.15, p = .29). This finding provides support that anti-HBc status was partially mediating the relationship between HCV and sustained attention.

The impact of additional confounds was assessed using ANCOVAs after determining that endorsement of cocaine use was significantly associated with poorer delayed verbal memory (r = -.19, p = .04) and the presence of liver dysfunction was significantly associated with poorer attentional set-shifting (r = -.19, p = .05)[12]. In regards to delayed verbal memory, it was determined that neither the main effect of HCV status ($F_{(1, 74)}$ = .03, p = .87, η^2 = .00) nor cocaine use ($F_{(1, 74)}$ = 1.07, p = .31, η^2 =

[11] Non-significant point biserial correlations between HBV surface antibody results and neurocognitive functioning supported the notion that it was exposure due to HBV infection and not vaccination status that led to poorer neurocognition. Only two participants had an active HBV infection and this was also not significantly associated with neurocognitive functioning.
[12] ANCOVAs were run in a reduced sample with participants positive for anti-HBc excluded.

.31) were significantly associated with this neurocognitive domain. Similarly, neither the main effect of HCV status ($F_{(1, 73)}$ = 1.16, p = .29, η^2 = .02), nor liver dysfunction ($F_{(1, 73)}$ = .01, p = .91, η^2 = .00) were significantly associated with attentional set-shifting.

Lastly, it was found that better response inhibition was significantly associated with endorsement of IVDU (r = .20, p = .02), yet response inhibition was not associated with anti-HBc. As such, an ANCOVA was run in the sample including participants' positive for anti-HBc. The main effect of HCV status on response inhibition was not significant ($F_{(1, 129)}$ = .01, p = .93, η^2 = .00), however the effect of the covariate was significantly associated with response inhibition ($F_{(1, 129)}$ = 4.74, p = .03, η^2 = .04)[13].

[13] Follow-up point biserial correlations revealed that this association was only significant in the HCV-exposed group.

Chapter 9. Study 2 Discussion

The goal of Study 2 was to confirm the limited evidence suggesting a possible reversal of HCV-related neurocognitive deficits with spontaneous HCV eradication (i.e., without pharmacological intervention). Notably, our study extends on previous work by including a larger sample of persons with spontaneously cleared HCV and active HCV, by considering other viral infections (i.e., HIV, HBV, CMV, and HSV), and by studying this effect in marginalized persons with a multitude of risk factors for neurocognitive impairment (e.g., psychiatric illness, substance use, etc.). Unlike earlier studies (Forton et al., 2002; Lowry et al., 2010), we did not find any significant neurocognitive differences between well-matched individuals with spontaneously cleared HCV and active HCV. When comparing participants exposed to HCV (either cleared or active) to individuals with no lifetime HCV infection, we found that the HCV-no exposure group had more intact sustained attention relative to the HCV-exposed group. Nevertheless, this effect did not remain when statistically controlling for the confounding effects of HBV exposure (i.e., anti-HBc).

9.1. Neurocognition in HCV-Cleared Persons

The first hypothesis of the study, that persons with cleared HCV would present with more intact neurocognition compared to well-matched persons with active HCV, was not supported. The only significant group difference to emerge was on a measure of sustained attention with the HCV-active group performing better than the HCV-cleared group after excluding participants with non-normal liver functioning. A similar finding emerged in a study of women, such that the HCV-active group displayed better sustained attention compared to a healthy comparison group (no history of HCV exposure; Lowry et al., 2010) with the authors positing that this finding was likely an invalid result based on the small sample sizes employed in their study. Similarly, the

results in our study did not withstand correction for multiple comparisons and therefore may be spurious.

9.2. Neurocognition in the HCV-No Exposure Group

In line with the second hypothesis, the HCV-no exposure group demonstrated more intact neurocognition compared to the HCV-exposed group. However, many of these differences were not statistically significant, with the exception of better sustained attention. Nevertheless, after considering the widespread comorbidities experienced by the HCV-exposed participants in this study, our results indicate that anti-HBc status is partially mediating the relationship between sustained attention and HCV-infection.

9.3. The Impact of Hepatitis B Virus on Neurocognition

The emergence of a significant negative association between positive anti-HBc status and greater neurocognitive impairment (e.g., sustained attention, verbal learning and memory, overall cognition) was an unexpected finding, albeit instrumental in understanding the relationship between neurocognition and HCV in our sample. Importantly, the above-noted associations were only found with the core-antibody serological result and not the surface antibody test (i.e., indicative of vaccination to the virus), supporting the notion that *infection* by HBV may be detrimental to aspects of neurocognitive functioning. This finding contributes to the paucity of research evaluating the impact of HBV-infection on brain functioning and subsequently neurocognition (Gale et al., 2016; Karaivazoglou et al., 2007; Severtson et al., 2012; Yoffe & Noonan, 1992). Also notable were the findings that a positive anti-HBc result was significantly associated with HIV positive serostatus, liver dysfunction, heroin and cocaine use, and IVDU, suggesting that in our sample, and possibly extending to other marginalized samples, HBV is a proxy measure for these other risk factors. In other words, an anti-HBc positive result captures an increased likelihood of the above noted risk factors for neurocognitive impairment. Overall, the

current findings promote further examination into the effects of HBV on neurocognitive functioning.

9.4. Application of the Current Findings

Although the study hypotheses were not supported, several suggestions for the application of these findings are offered. First, it is possible that spontaneous clearance of HCV is not potent enough to reverse deficits in the context of numerous modifiers of neurocognition. As such, HCV-medication implementation in marginalized populations may be necessary. Indeed, with more traditional treatment options (e.g., interferon and ribavirin; IFN/RBV), approximately 50% of HCV-individuals demonstrate viral eradication (McNutt et al., 2012; Zhang et al., 2015), with several studies noting improved neurocognitive performance in persons who responded to the intervention (Byrnes et al., 2012; Kraus et al., 2013; Thein et al., 2007). Unfortunately, IFN-related side-effects are common, including fatigue, depression, “brain fog” (Lam, Jeffers, Younoszai, Fazel, & Younossi, 2015), and objective neurocognitive impairments (Cattie et al., 2014; Reichenberg, Gorman, & Dieterich, 2005). Promisingly, newer IFN-free therapeutic strategies (e.g., sofosbuvir and ledipasvir) have been developed and are accompanied by consistently high rates of sustained serological response (90%), fewer notable side-effects, lower pill burden, and shorter treatment duration. These benefits have been found in persons with complex medical needs, including HIV/HCV co-infected individuals (Fazel et al., 2015). With this in mind, newer interventions could be an effective avenue for treatment of marginalized persons with comorbid psychiatric and substance use histories (Hauser & Kern, 2015).

Second, our results demonstrate that individuals not exposed to HCV present with far fewer risk factors (e.g., viral co-infection, substance use, etc.) for neurocognitive impairment compared to groups exposed to HCV, which may inform harm reduction implementation. If HCV infection can be prevented, or at the very least managed, it is possible that fewer additional risk factors will emerge, potentially limiting neurocognitive impairment.

Third, our results revealed that in addition to HCV, exposure to other viruses (e.g., HBV) and select drug use (e.g., cocaine) were selectively associated with lowered neurocognitive functioning. These findings underscore the importance of co-treating these comorbid conditions in marginalized persons. Although cocaine and methamphetamine use are often cited as reasons for denying HCV-treatment access (Alavi et al., 2014), research suggests that individuals with HCV and comorbid psychiatric and substance use can be treated effectively (Hauser & Kern, 2015). Indeed, simultaneous treatment of addiction can improve HCV treatment results (Dimova et al., 2013). Moreover, vaccination programs and psychoeducation around the adverse link between HBV and injection drug use have been recommended (Garfein et al., 2004; Vogt et al., 2006).

9.5. Limitations

As with all studies, limitations should be noted. The sample used to examine the effect of spontaneous clearance of HCV on neurocognition was of convenience. Participants were recruited into the original study based on their residency in SRO hotels, not based on their HCV status. Likewise, the impact of HBV status on neurocognitive functioning was neither the intended purpose of this current study nor the aim of the original, larger study. Therefore, not all participants with anti-HBc reactivity were further confirmed with other HBV markers (i.e., the full HBV panel at baseline blood work), which could result in a false positive result of exposure to HBV for a proportion of participants. Nevertheless, as discussed by Grob et al. (2000) the proportion of false positive results is low in high prevalence groups, such as our sample where rates of HIV and/or HCV co-infection are elevated.

Secondly, the numerous confounds (e.g., liver functioning, HBV, etc.) identified in this study may have limited detection of the direct effects of HCV on neurocognitive functioning. Nevertheless, this complexity in comorbid conditions is apt to generalize to other groups of marginalized persons, where rates of substance use and viral infections are ubiquitous. This complexity in multimorbidity also likely speaks to the difficulty faced by health care professionals in effectively treating persons with HCV.

Lastly, given that neuropsychological assessments were only one component of the comprehensive baseline assessment in the larger, original study, the battery was designed to be brief. As indicated in Study 1, the conclusions about neurocognition are based on, and limited to, the tests used to measure the different aspects of neurocognition. Also, the reliability and validity of the inferences made from these measures could impact the findings. It is possible that select areas of neurocognitive impairment were not inspected, reducing the potential to detect group differences. Nonetheless, the neurocognitive measures chosen for inclusion have been shown to be sensitive to the effects of HCV on neurocognitive functioning (Byrnes et al., 2012; Letendre et al., 2005; Majer et al., 2008; Vigil et al., 2008).

9.6. Conclusions

Our findings suggest that reversal of neurocognitive impairments resulting from spontaneous clearance of HCV may not be achieved in marginalized samples with high rates of substance use, viral infections, and psychiatric illness. In contrast, select neurocognitive impairments were observed with HCV-exposed persons compared to a HCV-no exposure group. Nevertheless, when comorbid conditions were considered, in particular HBV, these effects did not remain significant, highlighting the importance of detection and treatment of other viral infections. In line with this, more research is needed in understanding the effect of different viral infections on neurocognitive functioning. Most research in this area has been conducted on HIV and HCV though our results point to the possible detrimental impact of HBV on neurocognition. Lastly, with the advent of newer HCV treatment options that may be better tolerated by marginalized persons, examination of the impact of these medications on neurocognitive functioning is merited.

Chapter 10. General Discussion

Two studies were conducted with the overall aim of better understanding the interrelationship between viral infections and neurocognition in a sample of marginalized people living in SRO hotels in Vancouver's DTES. In study one, SEM was employed to assess the relative impact of viral infections on neurocognitive functioning in the context of other health factors that are determinants of impairment, namely psychiatric illness, substance use, and medical and neurological conditions. An additional purpose was to determine whether health factors, in particular viral infections, were subsequently related to HSU. It was found that greater viral infection exposure and increasing psychiatric symptom severity were comparably associated with neurocognitive dysfunction; however, when including individuals with active HCV over exposure to HCV, the viral infection construct was the strongest predictor of neurocognitive deficits. Substance use had a smaller magnitude association with neurocognition, with a notable positive association between increasing substance use and neurocognition. Additional analyses revealed that this relationship was driven by a significant association between greater days of heroin use and faster processing speed, and as such, the substance use construct was reconceptualised as more frequent opioid use/less frequent alcohol and marijuana use. Overall, given the small effect size, the impact of substance use should be considered cautiously. Viruses, yet not psychiatric symptoms or substance use, were associated with HSU overall. Unexpectedly, viral infections were associated with more ambulatory visits, but fewer hospitalizations. The relationship between viral infections and HSU was not mediated by neurocognition.

Study two focused on comparing neurocognitive functioning in participants with cleared versus active HCV to clarify whether spontaneous clearance of HCV is associated with reversal of neurocognitive deficits in marginalized persons. Using a matched group design we found no significant neurocognitive differences between HCV-active versus HCV–cleared groups. The active and cleared groups were

subsequently combined into an HCV-exposed group and compared to a group with no history of exposure to HCV. The HCV-no exposure group displayed better sustained attention and marginally better learning and memory relative the HCV-exposed group. However, these effects did not remain after removing variance associated with HBV, suggesting that this latter virus was partially mediating the relationship among HCV and neurocognitive deficits.

10.1. Contributions

The current findings offer several contributions to understanding the complex interplay between viral infections, neurocognition, and HSU. To the best of our knowledge this is one of the first studies to comprehensively examine the impact of multiple viral infection exposures on neurocognition in marginalized persons. Indeed, we found that greater exposure to viral infections was associated with poorer neurocognition. Neurocognitive impairment in a marginalized sample could result in unfortunate outcomes, including inadequate advocacy for better living situations or difficulty fully understanding the impact of poor health status on overall well-being and survival. Establishing that neurocognitive impairment exists in marginalized persons provides additional impetus to successfully treat all potential predictors of neurocognition (i.e., psychiatric symptoms, viral infections, etc.).

Second, our findings highlight the need to more thoroughly evaluate the effects of a broader range of viral infections on neurocognitive functioning. In addition to HIV and HCV, viral infections such as HBV, CMV and HSV are prevalent in marginalized populations. Further, the results from studies one and two point to a significant relationship between exposure to HBV and neurocognitive impairment. Notably, HBV has received limited research in regards to impact on neurocognition and our results indicate that further investigation is warranted.

Third, to date only one other study to our knowledge has examined the association between neurocognition and health care use in virally infected persons (i.e., HIV+; Okonkwo et al., 2008). Our work greatly added to this literature by including objective measures of neurocognition and by elucidating barriers to care at

both personal and structural levels. Importantly, our findings suggest that neurocognition is not a personal barrier to accessing care, which may underscore the marginalization of this sample. Nevertheless, our findings point to evidence of structural barriers, in that health services were selectively utilized. At the level of the health care system, marginalized persons with viral infections, but not psychiatric illness or substance use, are seeking out care, in particular ambulatory services for physical health issues. It is possible that persons with mental health or substance-related concerns do not feel adequately treated within the available health care system; therefore they do no access services in any capacity (i.e. emergency room visits or ambulatory appointments).

Lastly, although our findings did not support the idea that spontaneous clearance of HCV would result in a subsequent reversal of HCV-associated neurocognitive impairment, our results provide further evidence that exposure to HCV conveys adverse health. In identifying a control group (no exposure to HCV) to compare to HCV-infected individuals, including those with active and cleared infection, several confounds emerged. Individuals exposed to HCV had significantly higher rates of HIV, HBV, HSV, liver dysfunction, cocaine and heroin use, and IVDU. This is a significant health concern for at least a couple reasons. First, many of the above-noted comorbid factors are often cited as restrictions to people receiving treatment for HCV (Alavi et al., 2014; Hauser & Kern, 2015). Second, the comorbid factors are likely independently contributing to poorer quality of life, which may make these individuals less motivated to seek out appropriate health care. These findings add to the above contributions in that treatment for viral infections, along with other health factors, is of utmost importance in marginalized populations.

10.2. Implications

A profound implication of our findings is that viral infections and psychiatric illness are significant contributors to neurocognitive impairment in a marginalized sample. Unfortunately, treatment interventions are grossly inadequate for these health factors. For instance, 60/63 participants in our study with HIV that were enrolled in a Provincial (i.e., British Columbia) drug treatment program had documentation of

successful viral suppression after starting treatment, yet, only 38 participants were continuing with antiretroviral therapy at baseline assessment (Jones et al., 2015). This points to an effective treatment but a poor delivery platform, in that the treatment works (i.e., viral suppression) but adherence is less than ideal.

In contrast to HIV, none of the participants in our study with active HCV had received the orally active, curative antivirals (Jones et al., 2015). Fifty-seven participants had active HCV with evidence of hepatic fibrosis, and all were untreated. Of all participants in our study that were exposed to HCV, only 19/181 were ever treated with an IFN-based intervention, with effectiveness (i.e., qPCR-negative results) of treatment only found in 47% (Jones et al., 2015). Unlike HIV, the current treatment options for HCV in our sample are both ineffective and poorly delivered. Notably, application of IFN-free direct acting antivirals as prevention is a feasible approach to reducing continued burden of HCV-related disease (Martin et al., 2013).

Education is also integral to treatment and better delivery of effective HCV medications. For instance, within community pop-up clinics in several DTES sites (e.g., InSite, a SIF), it was determined that less than half (45%) of HCV-positive persons surveyed were aware that there was a cure for HCV, yet 80% would consider HCV treatment if offered (Conway et al., 2015). Evidently, barriers to HCV-treatment extend from the individual (i.e., lack of knowledge regarding treatment availability) to structural barriers ingrained in the healthcare system (i.e., cost of medication, pre-conceived notions around treating HCV, etc.; Conway et al., 2015).

Regarding treatment for psychiatric symptoms, about one-third of our study participants with psychosis (31.8%) were prescribed antipsychotic medication. However, no difference was found in symptom severity in those treated versus not treated (Jones et al., 2015). As with HCV, the current treatment options for psychosis were ineffective and far from universally applied. This may help clarify the finding that increasing psychiatric symptom severity is not associated with HSU in our sample, in that marginalized persons may not see the benefit to seeking out treatment – both acutely in emergency care or in outpatient services.

Collectively, considerably more work needs to be done in delivering effective interventions and providing an environment in which medications are adhered to. Marginalized persons may be best served within interdisciplinary team models where treatment for viral infections, psychiatric illness, and substance use can be equivalently addressed. Importantly, psychiatric illnesses (e.g., schizophrenia, depression, SUD) should no longer preclude individuals from being treated for HCV, given that psychiatric symptoms are less likely to emerge with the newer IFN-free medications (Hauser & Kern, 2015). Moreover, individuals concurrently treated for HCV and substance use/addiction (compared to those not being treated for SUD) had higher rates of HCV treatment completion (Diminova et al., 2013). The availability of multiple support services (e.g., needle exchange, counselling for risk reduction, psychological treatment, and educational intervention) during HCV treatment contributes significantly to increased treatment completion rates for substance use (Diminova et al., 2013). Viral infection prevention and treatment will also need to be expanded beyond the focus on HIV and HCV, including HBV. Along with implementation of HBV vaccinations to people living in the DTES, education should also be provided regarding transmission of HBV via sharing of drug equipment (Vogt et al., 2006).

10.3. Limitations

As with all research, several limitations emerged and those presented here generally reiterate the limitations described in Study 1 and Study 2. First, the generalizability of the findings is limited to similar marginalized samples with multiple comorbid risk factors for neurocognitive impairment. Second, the current research was conducted within the larger HOTEL study, and as such, data was limited to what had already been collected. Nevertheless, given that participants were followed and assessed monthly, and evaluated within the context of multiple disciplines (i.e., neuropsychology, psychiatry, neurology, radiology, etc.), a vast amount of data was collected and available. Further, the goals of Study 1 and 2 aligned with components of the mandate of the larger study, in that we examined cognitive dysfunction and the related factors that may contribute to those deficits, along with elucidating access to health care services. Third, some of the data collected was via self-report rather than

objective measurements (i.e., recent substance use, health care utilization, history of diabetes, etc.). Nonetheless, for several of these variables we were able to confirm concordance with objective measures (i.e., high reliability between self-report substance use and results from urine drug screens; Jones et al., 2013). Further, data pertaining to HIV was limited to antibody tests, although viral loads may be more accurate indicators of disease severity, including neurocognitive dysfunction (Devlin et al., 2012; Giesbrecht et al., 2014). Lastly, the neurocognitive battery employed in this study was designed to be brief given the breadth of data being collected overall from each participant. It is possible that areas of neurocognitive impairment were not identified. That being said, with the short battery employed, we were able to detect impairment in this sample.

10.4. Future Directions

The current findings provide the framework for continued research in understanding the links between health factors and neurocognition, and the subsequent impact on healthcare access. We found a significant relationship between increasing viral infections and greater ambulatory care visits. However, the question remains as to what initially brings these patients to outpatient services? In other words, what are the primary concerns or afflictions that lead a person to seek out medical treatment before that ailment becomes severe enough to warrant acute, emergency services? Additionally, when these individuals do see a medical professional in outpatient care, what issues are being treated? Are they being optimally treated for all emergent concerns or are issues being overlooked? Answers to these questions will be integral to tailoring medical care to the health needs of marginalized persons and ensuring effective treatment delivery. For instance, our findings did not indicate that neurocognition was a personal barrier to seeking out treatment; yet it is possible that neurocognitive deficits could be impacting what information is being disclosed by the patient in ambulatory care. If this latter idea is supported it may point to implementation of aides to reduce neurocognitive impairment from emerging in an outpatient setting (e.g., the use of symptom checklists to cue retrieval of concerns if memory is an issue). Further, building on the final limitation described earlier, it is possible that specific components of neurocognitive

dysfunction contribute to inefficient use of outpatient services, but were not assessed in this current work. As such, future work should be done to evaluate a broader range of neurocognitive domains (e.g., planning and organizing, or prospective memory), to further elucidate whether specific areas of neurocognitive impairment contribute to the relationship between viral infections and HSU.

Future research into better understanding the neurocognitive effects of select viral infections is also indicated. In particular, our findings demonstrated that HBV is significantly contributing to neurocognitive impairment in a marginalized sample. Very few studies have examined this relationship; however, given the high rates of co-infection between HCV and HBV in marginalized populations, a better understanding of the role of HBV on brain functioning and neurocognition is imperative.

Our findings revealed that spontaneous treatment of HCV may not be enough to reverse HCV-associated brain effects in marginalized persons. It is possible that pharmaceutical interventions are necessary. The effects of older, IFN-based HCV medications on neurocognition have been examined, yet no studies to our knowledge have evaluated the neurocognitive consequences related to IFN-free medications. Based on the research pointing to better tolerance of these newer HCV treatments in marginalized persons, it will be essential to assess the impact on neurocognition to determine if this may be a barrier to treatment (i.e., if IFN-free interventions are associated with neurocognitive impairment).

10.5. Final Conclusion

Viral infections pose a significant threat to neurocognition in marginalized persons. Insufficient treatment of viral infections is a public health concern that needs to be addressed. Viral infections are associated with adverse health overall, and eradicating infections could help to reduce co-existing medical conditions. In addition, the current work added to a growing body of research examining health service use in marginalized samples, suggesting that ambulatory care is being utilized; however, in conjunction with other work being done in the HOTEL study, it appears that viral

infections are not being adequately targeted, nor are other health factors experienced by marginalized persons (e.g., psychiatric illness).

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Appendix A. Pre-screening for Possible Variables in SEM Model.

	Neurocognition			
Variable	Processing Speed	Verbal Memory	Sustained Attention	Set-Shifting
Psychiatric Symptoms				
Mood disorder	.02	-.04	-.10	.02
Anxiety disorder	.07	-.02	.01	.05
BDI[a]	-.02	.11	.03	.00
Acute substance use				
Alcohol	-.00	.04	.01	.05
Marijuana	.07	.02	.11	.03
Cocaine	-.04	-.02	-.02	-.03
Opiate	.09	.07	.03	.07
Methamphetamine	.10	.12	.10	.10
Methadone	-.02	-.09	-.03	-.04
Neurological				
MRI.TBI[b]	-.05	-.02	-.02	-.08
Parkinsonism[c]	-.09	-.05	-.08	-.10
Dyskinesia	-.20**	-.06	-.20**	-.16*
Akathisia	-.01	.03	-.07	.06

Note. Values represent Pearson correlations (*r*); n = 254 unless otherwise specified. [a]n = 238; [b]n = 223; [c]n = 251; BDI = Beck Depression Inventory; MRI.TBI = MRI confirmed traumatic brain injury.
*$p < .05$; **$p < .01$.

Appendix B. Comparison of Participants Included and Excluded in Study 1

Characteristic	Included	Excluded	test-statistic	p-value
Demographics				
Age (mean years; SD)	43.01; 9.35	43.84; 9.99	t = .72	.47
Education (mean years; SD)	10.33; 2.36	10.02; 2.45	t = -1.09	.28
Sex (% Female; n)	20.1; 51	25.6; 30	χ^2 = 2.29	.13
Viral Infections				
HIV (% positive; n)	14.2; 36	24.0; 24[a]	χ^2 = 4.71	.03
HCV (% positive; n)	69.3; 176	64.2; 61[b]	χ^2 = .48	.49
HBV (% positive; n)	39.4; 100	43.3; 42[c]	χ^2 = .53	.47
CMV (% positive; n)	66.9; 170	66.7; 64[d]	χ^2 = .002	.96
HSV (% positive; n)	89.8; 228	86.5; 83[e]	χ^2 = .71	.40

Note. Included N = 254; Excluded N = 117 unless otherwise specified; SD = standard deviation; HIV = human immunodeficiency virus; HCV = hepatitis C virus (antibody test); HBV = hepatitis B virus (core antibody test); CMV = cytomegalovirus; HSV = herpes simplex virus; [a]n = 100; [b]n = 95; [c]n = 97; [d]n = 96; [e]n = 96.

Appendix C. Asscociations between neurocognitive performance with demographic and medical/neurological variables

	Neurocognition			
Variable	Processing Speed	Verbal Memory	Sustained Attention	Set-Shifting
Demographic				
Sex	.10	.06	.06	-.16**
Age	-.10	-.11	-.06	-.12
Education	.15*	.10	.14*	.08
Medical/Neurological				
MRI.CVA	-.01	.07	-.05	-.01
Diabetes	-.13*	-.11	-.06	-.14*
Cholesterol	.02	.01	.15*	.01
Liver Functioning	-.07	.02	-.02	.00
Heart Disease	-.06	-.08	.01	.06
Dyskinesia	-.20**	-.06	-.20**	-.16**

Note. Included N = 254; values represent Pearson's *r*; MRI.CVA = MRI confirmed evidence of cerebrovascular accident; $^{*}p < .05$; $^{**}p < .01$.

Appendix D. Additional Analyses: Opioid Use and Processing Speed

Three similar hierarchical linear regression analyses (HLRA) were run to assess whether MMT, alcohol, or marijuana were moderating the relationship between more frequent heroin use and faster processing speed. The HLRA included four blocks of variables, which represented the factors and related indicator variables that remained in the final SEM model. Psychiatric symptom variables were entered in the first block, followed by viruses, then substances use, and lastly the corresponding interaction term.

Heroin and MMT

On the first block, psychiatric symptoms explained 3.9% of the variance in processing speed ($F_{(3,\ 250)} = 3.41$, $p = .02$). On block two, the viruses explained an additional 2.7% of the variance ($\Delta F_{(4,\ 246)} = 1.76$, $p = .14$), however this change was not significant. Subsequently, substance use, entered on block three, explained 4.2% of the variance in processing speed ($\Delta F_{(4,\ 242)} = 2.86$, $p = .02$), which was a significant change. Lastly, the interaction term between heroin and MMT did not explain any proportion of the variance (0.0%) in processing speed ($\Delta F_{(1,\ 241)} = .05$, $p = .82$), indicating that MMT was not moderating the relationship between heroin and processing speed. The final model was significant ($F_{(12,\ 241)} = 2.44$, $p = .01$), accounting for 10.8% (6.4% adjusted) of the variance in processing speed. Of all the variables included, only Negative Symptoms/Hostility (F2; β = -.20, $p = .01$), HBV (β = -.18, $p = .01$), and heroin (β = .20, $p = .01$) were significant predictors of processing speed.

Heroin and Alcohol

The results relating to the first three blocks were identical to those presented above. The interaction term between heroin and alcohol did not explain any proportion of the variance (0.0%) in processing speed ($\Delta F_{(1,\ 241)} = .17$, $p = .68$), indicating that alcohol was not moderating the relationship between heroin and processing speed. The final model was significant ($F_{(12,\ 241)} = 2.45$, $p = .01$), accounting for 10.9% (6.4% adjusted) of the variance in processing speed. Of all the variables included, only Negative

Symptoms/Hostility (F2; β = -.20, p = .01), HBV (β = -.18, p = .01), and heroin (β = .18, p = .02) were significant predictors of processing speed.

Heroin and Marijuana

The first three blocks were identical to those presented above with MMT and heroin. The interaction term between heroin and marijuana did not explain any proportion of the variance (0.0%) in processing speed ($\Delta F_{(1, 241)} = .45$, p = .50), indicating that marijuana was not moderating the relationship between heroin and processing speed. The final model was significant ($F_{(12, 241)} = 2.45$, p = .004), accounting for 11.0% (6.6% adjusted) of the variance in processing speed. Of all the variables included, only Negative Symptoms/Hostility (F2; β = -.20, p = .01), HBV (β = -.18, p = .01), and heroin (β = .16, p = .04) were significant predictors of processing speed.

Appendix E. Comparison of Participants Included and Excluded in Study 2

Characteristic	Included	Excluded	test-statistic	p-value
Demographics				
Age (mean years; SD)	44.65 (7.84)	42.42 (10.26)	t = -2.35	.03
Education (mean years; SD)	10.31 (2.29)	10.24 (2.38)	t = -.27	.79
Sex (% Female; n)	35.0; 48	13.7; 32	χ^2 = 23.31	p < .01
Viral Infections				
HCV duration (mean years; SD)	14.88 (7.62)[a]	12.40 (9.59)[b]	t = -1.87	.06
HIV (% positive; n)	19.0; 26	16.0; 34[c]	χ^2 = .53	.28
HBV (% positive; n)	36.5; 50	42.9; 90[d]	χ^2 = 1.39	.14
CMV (% positive; n)	69.3; 95	65.1; 136[e]	χ^2 = .68	.24
HSV (% positive; n)	92.7; 127	86.1; 201	χ^2 = 3.58	.04

Note. Included N = 137; Excluded N = 234 unless otherwise specified; SD = standard deviation; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HBV = hepatitis B virus (core antibody test); CMV = cytomegalovirus; HSV = herpes simplex virus; [a]n = 69; [b]n = 134; [c]n = 213; [d]n = 210; [e]n = 209.

Appendix F. Managing Confounding Factors: Associations between Neurocognition and Comorbid Conditions in HCV-exposed vs. HCV-no exposure groups

	Neurocognition						
Comorbid Condition	Processing Speed (n = 125)	Response Inhibition (n = 125)	Verbal Learning (n = 120)	Verbal Memory (n = 120)	Sustained Attention (n = 115)	Set-Shifting (n = 115)	Overall Cognition (n = 103)
HIV	-.12	-.05	-.08	-.12	-.16	-.10	-.12
HBV	-.16	-.10	-.21*	-.21*	-.26**	-.21*	-.29**
HSV	.09	.07	.02	.05	-.12	-.05	-.02
Liver Function	-.07	.01	.11	.05	-.12	-.19*	-.12
Heroin	.07	.08	.04	-.08	-.02	.02	.06
Cocaine	-.10	-.15	-.02	-.19*	-.17	.03	-.13
IVDU	.14	.20*	.05	-.02	-.02	.06	.05

Note. Values represent point biserial correlations; HIV = human immunodeficiency virus; HBV = hepatitis B virus; HSV = herpes simplex virus; IVDU = intravenous drug use; $^{*}p < .05$; $^{**}p < .01$.

Appendix G. Neurocognitive Comparison between HCV-exposed and HCV-no exposure groups: Excluding anti-HBc Positive Participants.

	HCV-Exposed			HCV-Not Exposed					
Cognitive Domain	M	SD	N	M	SD	N	t	p	E.S.
Processing speed	62.60	12.56	40	59.88	13.72	43	-.94	.35	-.21
Response Inhibition	37.42	10.68	40	33.44	10.28	43	-1.73	.09	-.38
Verbal Learning	18.76	4.71	41	19.76	6.16	41	.83	.41	.18
Verbal Memory	6.07	2.24	41	6.61	3.24	41	.87	.39	.19
Sustained Attention	.87	.07	37	.88	.06	40	.80	.42	.15
Set-shifting[a, b]	50.33	46.70	36	56.88	40.60	40	-1.27	.21	-.15
Overall Cognition	.15	.59	33	.13	.75	35	-.14	.89	-.03

Note. M = mean; SD = standard deviation; E.S. = effect size (Hedges' *g*); [a]Values for IED Total error adjusted are untransformed, but the independent t-tests were run on log10 transformed data; [b]higher score (more errors) represents worse performance.