Heroin Use, Traumatic Brain Injury, and Schizophrenia Predict Everyday and Social Functioning in Marginally Housed Persons: Direct Effects and Mediation by Neurocognition

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Ethics Statement

The author, whose name appears on the title page of this work, has obtained, for the research described in this work, either:

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Abstract

Multimorbid illness, including substance use, psychiatric illness, viral infection, and traumatic brain injury (TBI), is prevalent in marginally housed persons, but it is unclear how these problems influence everyday and social functioning. We conducted mediation analyses in 210 participants in order to evaluate the effects of substance use, psychiatric illness, viral infection, and traumatic brain injury on predicting 6-month follow-up ratings of functioning, and to examine whether neurocognitive performance significantly mediated the relationship between these health characteristics and ratings of functioning. Neurocognition, alongside positive and negative symptoms, explained 47% of the effect of schizophrenia on functioning and 11% of the effect of TBI on functioning. Additionally, greater heroin use frequency was significantly associated with lower ratings of functioning, but this effect was not mediated by neurocognition. Our findings highlight the role of neurocognition in mediating the relationship between illness and functioning in the marginally housed, and inform treatment targeting toward specific morbidities in populations with complex health issues.

Keywords: substandard housing; mediation analysis; everyday functioning; neurocognition; schizophrenia; traumatic brain injury; substance use

Dedication

For Mom and Dad – these words are really your words, because only with your enormous sacrifice, hard work and love, could I enjoy the opportunities and blessings I have now. Thank-you from the bottom of my heart.

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Introduction

In most North American cities, single room occupancy hotels (SROHs) represent the last resort for housing for low-income individuals (Shannon, Ishida, Lai, & Tyndall, 2006), despite the fact that living conditions are considered highly substandard (BC Ministry, 1994; Foley, 1998). Living in SROHs, compared with residence in more stable housing, is associated with severe illicit drug use, viral infections, higher rates of emergency room use, recent incarceration, and having been a victim of physical assault (Shannon, Ishida, Lai, & Tyndall, 2006). Among adults experiencing unstable housing or homelessness, alcohol and substance dependence, psychotic illness, and major depressive disorder are common (Fazel, Kohsla, Doll, & Geddes, 2008), and comorbidity of polysubstance use and major mental illness approaches 80% (Koegel, Sullivan, Burnam, Morton, & Wenzel, 1999).

Our research group determined that a large sample of SROHs residents in Vancouver, Canada experience a high rate of multimorbid health issues, including substance dependence (95.2%), Hepatitis C (70.3%), and psychotic illness (47.4%; Vila-Rodriguez et al., 2013). Nearly 64% of participants also endorsed a history of serious head or facial injury. Hepatic fibrosis and psychosis were also found to be associated with a 8-fold increased likelihood of mortality in this sample (Jones et al., 2015). Unsurprisingly, living with multiple illnesses was also significantly related to lower ratings of psychosocial functioning, as measured by the Role Functioning Scale and the Social and Occupational Functioning Assessment Scale (Vila-Rodriguez et al., 2013).

Despite the growing emphasis in many healthcare fields to improve functional outcome with treatment, the differential impact of these various health problems on impairing functioning has never been elucidated in a marginally housed sample. Yet, deficits in functioning associated with physical and mental disorders are increasingly recognized as valuable treatment goals that are associated with global wellbeing (World Health Organization, 2002; Reed, Spaulding, & Bufka, 2009). Substandard functioning is an issue of critical importance in both clinical research and policy development, as functional disability is associated with both personal burden and tangible costs to employers and society. Substance use, psychiatric illness, viral infection, and traumatic brain injury (TBI) have all been independently linked to impaired real world functioning, and there is growing evidence that cognitive impairment may represent a significant

pathway through which these overt illnesses influence functional outcomes. In the current study, we evaluated the effects of substance use, psychiatric illness, viral infection, and traumatic brain injury on predicting 6-month follow-up ratings of everyday and social functioning, and examined whether neurocognitive performance significantly mediated the relationship between these health characteristics and ratings of functioning.

Empirical evidence from substance use, psychiatric illness, traumatic brain injury, and viral infection research suggests that the modelling of causal pathways between illnesses and functional outcomes should examine the mediating, or explanatory, role of neurocognition. In terms of substance use disorders, there is a clear relationship between substance misuse and functional impairment, as indicated by the diagnostic criteria of substance use disorders (Diagnostic and Statistical Manual of Mental Disorders, 5th Ed.; American Psychiatric Association, 2014), which references deficits in role performance and harm to social relationships and activities. Importantly, neurocognition is influenced by heavy substance use and is apt to be a pathway by which drug use impacts real world function. Research shows medium to large effect sizes for chronic alcohol and methamphetamine use on nearly all neurocognitive domains (Scott et al., 2007; Stavro et al., 2012), impairments in verbal episodic memory and executive function in cannabis users (Crane, Crane, & Mason, 2011; Crane, Schuster, Fusar-Poli, & Gonzalez, 2013), negative effects on verbal working memory, cognitive impulsivity and flexibility in opiate users (Baldacchinoa, Balfoura, Passettib, Humphrisc, & Matthews, 2012), and impaired attention, visual and working memory, and executive functioning in cocaine users (Jovanovski, Erb, & Zakzanis, 2005).

An emergent literature reveals that substance-using persons with greater cognitive impairment have more negative real world outcomes. Within substance dependent persons or regular substance users, poorer cognitive functioning is a significant predictor of worse real world performance. Examples include the effects of methamphetamine-related neurocognitive impairment on unemployment status, cognitive complaints, and greater dependence in activities of daily living (Weber et al., 2012; Sadek, Vigil, Grant, Heaton, and the HNRC Group, 2007), the effects of cocaine-related alterations in social reward processing on reduced social network size (Preller et al., 2014ab), and the effects of cannabis-related impairments in decision-making, risk-taking, and increased risky sex practices (Schuster, Crane, Mermelstein, & Gonzalez, 2012). While past research has established the relationship between neurocognition and real world outcomes in specific substance-using samples, the current study addresses gaps in the

literature by identifying which substances are most strongly related to functional outcomes in a multimorbid, polysubstance-using sample, and by definitively examining whether neurocognition is a pathway by which substance use negatively impacts functional outcome.

Psychiatric illness has become increasingly recognized as a significant contributor to rates of worldwide disability, and the adverse effects of mental disorder on real world functioning have been robustly linked to changes in cognition. Mental illness is associated with similar or higher levels of disabilities across multiple domains of functioning (e.g., daily living activities, social activities participation, work-loss days) compared to physical disorders such as arthritis and heart disease (Buist-Bouwman et al., 2005; Buist-Bouwman et al., 2006). Mood disorders and schizophrenia in particular are linked to functional impairment, and are cited as two of the thirty leading causes of worldwide disability due to disease (Murray & Lopez, 1997).

Importantly, worse cognitive performance plays a significant role in the relationship between mental illness and functional impairment. In schizophrenia research, neurocognitive ability and psychiatric symptoms are thought to be the main drivers of functional disability (Breier, Schreiber, Dyer, & Pickar, 1991; Rajji, Miranda, & Mulsant, 2014; Carbon & Correll, 2014). Both global scores of neurocognitive ability and performance in individual cognitive domains have been consistently linked with functional outcomes and show large effect sizes (Goldberg & Green, 2002; Green, Kern, & Heaton, 2004; Fett et al., 2011). Patients with depression also show moderate deficits in executive function, memory, and attention, relative to controls (Rock, Roiser, Riedel, & Blackwell, 2014); even with the remission of mood symptoms in depression, cognitive impairment is associated with functional disability (Jaeger, Berns, Uzelac, & Davis-Conway, 2006). Bipolar disorder is also associated with moderate negative effects on executive function, verbal learning and memory, attention, and response inhibition (Robinson et al., 2006). As to our knowledge, such relationships have not been previously reported in the literature, we aimed to discern which psychiatric illnesses were most strongly associated with poorer functioning in a marginally housed sample, and to determine the contributions of neurocognition and psychiatric symptoms in mediating this relationship.

Similarly to substance-using and psychiatric populations, neurocognition may play an intermediary role between viral infection status and real world functioning in persons with viruses such as human immunodeficiency virus (HIV), Hepatitis C virus (HCV), Hepatitis B virus (HBV), cytomegalovirus (CMV), and herpes simplex virus (HSV). Infected macrophages

stimulating excitotoxic neuronal damage is thought to underlie the cognitive dysfunction often observed in HIV (Lindl, Marks, Kolson, & Jordan-Sciutto, 2010). HIV-related neuropsychological deficits are furthermore associated with worse performance on measures of functional ability, which predict poorer everyday functioning (Heaton et al., 2003; Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Doyle et al., 2013). Though to our knowledge, no previous studies have examined the influence of neurocognition on functional outcomes in persons with HCV or HBV, cognitive impairment has been observed in persons obtaining treatment for such infections (Lieb et al., 2006). Studies of cognitive function in chronic HCV patients report mixed findings, but suggested mechanisms through which HCV potentially contributes to cognitive degeneration include elevated levels of proinflammatory cytokines, associated with memory impairment (Senzolo et al., 2011).

Significant associations have also been found between higher levels of cytomegalovirus (CMV) antibodies and poorer cognitive functioning (Dickerson et al., 2014). Similar roles for inflammatory markers in the brain are posited for the relationship between CMV and poorer cognition (Dickerson et al., 2014; Kilgour et al., 2013). There is also some evidence that HSV infection is associated with cognitive impairment, though no links to functional outcome have been assessed (Fruchter et al., 2015; Prasad et al., 2012). The intermediary role of neurocognition as a mediating pathway through which viral infection influences real world functioning has never, to our knowledge, been directly assessed. We also examined associations between the presence of hepatic fibrosis or cirrhosis, indicative of poorer liver functioning associated with a more severe and chronic course of HCV or HBV infection, and ratings of functioning.

Finally, neurological injuries are also present within the current sample (Vila-Rodriguez et al., 2012). Notably, moderate to severe traumatic brain injury (TBI) adversely effects vocational functioning, social relationships, and quality of life (Temkin, Corrigan, Dikmen, & Machamer, 2009; Hoofien, Gilboa, Vakil, & Donovik, 2001), and is also associated with large impairments (d = -.74) on cognitive functioning (Schretlena & Shapiroa, 2009). Furthermore, neuropsychological test performance is related to concurrent ratings of functional outcome over the first year following a TBI (Spitz, Ponsford, Rudzki, & Maller, 2012). The current study assessed the role of MRI-defined TBI in predicting functional outcomes, as well determined the extent to which impaired cognitive performance mediated this relationship.

In sum, research indicates that neurocognition may play an important role as an intermediary factor between the presence of a variety of different health issues and their effects on real world functioning. As poorer neurocognition may be a pathway through which chronic substance use, psychiatric illness, viral infection, and TBI evoke worse functioning, we examined the extent to which neurocognition mediates, or explains, the relationship between these participants' health characteristics and their real world functioning. Our previous investigation of the health characteristics of the current SROH sample found that it is predominated by individuals with a substance dependence disorder and/or a viral infection, with a substantial proportion also suffering from psychotic and mood disorders (Vila-Rodriguez et al., 2013). Discerning which health characteristics are most strongly associated with functioning, and identifying a potential process through which functioning is impaired, is of urgent importance to this severely ill population.

The present study is novel in undertaking a comprehensive evaluation of the impact of the multiple health issues, such as substance use, psychiatric diagnoses, viral infection, and TBI, on 6-month follow-up ratings of real world functioning in a marginally housed sample. Secondly, we assessed the extent to which neurocognitive ability plays an intermediary role in explaining the relationship between these illnesses and their influence on real world functioning in a marginally housed sample. Real world functioning was assessed using a composite score consisting of participants' scores on the Social and Occupational Functioning Assessment Scale (SOFAS), a frequently used estimate of global functioning (Goldman, Skodol, & Lave, 1992), and the Role Functioning Scale (RFS), a rating scale of participants' level of independent self-care, working productivity, and quality of social relationships (Goodman, Sewell, Cooley, & Leavitt, 1993).

We hypothesized that more frequent use of heroin, crack cocaine, and methamphetamine would be associated with lower ratings of functioning at 6-month follow-up. Previous work from our group demonstrated that participants with greater frequency of crack cocaine and heroin use are at greater risk of mortality (Jones et al., 2013), and a large multicriteria decision analysis conducted by the Independent Scientific Committee on Drugs concluded that heroin, crack cocaine, and methamphetamine carry the greatest physical, psychological, and social harm to individual users (Nutt et al., 2010). In addition, we expected that the composite neurocognitive score would mediate the relationship between frequency of substance use and functional outcome. Secondly, we hypothesized that a diagnosis of a

psychotic illness would be associated with lower ratings of functioning at 6-month follow-up. As studies indicate that in addition to neurocognition, psychiatric symptoms are also associated with functioning (Velligan et al., 1997; Harvey et al., 1998; McGurk et al., 2000; Goldberg & Green; 2002), positive and negative symptoms were examined as mediators of functioning, alongside neurocognition, for the psychotic illness variable. Thirdly, we hypothesized that positive viral infection status as well as the presence of hepatic fibrosis or cirrhosis would be associated with poorer ratings of functioning that would be mediated by poorer neurocognition performance. In particular, HIV, HCV, CMV, and HSV have been associated with cognitive impairment (Lindl, Marks, Kolson, & Jordan-Sciutto, 2010; Lieb et al., 2006; Dickerson et al., 2014; Prasad et al., 2012). Fourthly, as TBI has been closely linked to both cognitive impairment and poorer real world functioning post-injury (Temkin, Corrigan, Dikmen, & Machamer, 2009; Hoofien, Gilboa, Vakil, & Donovik, 2001, Schretlena & Shapiroa, 2009), we hypothesized that the presence of MRI-defined TBI would be significantly predictive of poorer ratings of functioning at 6-month follow-up, and that this relationship would be mediated by poorer neurocognitive performance.

Methods

1.1.1. Study Design and Participants

379 participants were enrolled in an ongoing 10-year longitudinal study (Vila-Rodriguez et al., 2012). Participants were either recruited residents from four single room occupancy hotels (SROH) in Vancouver, British Columbia or were recruited from outside the downtown community courts (Jones et al., 2015). Eighty-percent of the DCC sample reported living in a SRO hotel at study entry (Jones et al., 2015). The inclusion criteria were SROH residency, ability to communicate in English, and ability to provide written informed consent. Participants were paid a modest honorarium for their time. Ethics was approved by the Clinical Research Ethics Board of the University of British Columbia Ethics and the Simon Fraser University Office of Research Ethics. All analyses were done with SPSS Version 22.0 (SPSS Inc.) and Preacher & Hayes' PROCESS Macro Version 2.15 for statistical moderation, mediation, and conditional process analyses. Analyses were conducted on 210 participants with complete data on all measures (Hayes, 2013); details on variables with missing data can be found in Table 5 in Appendix B. A description of the sample is provided in Table 1.

Table 1. Sample Characteristics (N = 210)

Characteristic	%	Mean (SD)	Median	Range
Gender	76.2 (M)			
Age (years)		43.4	44.0	25-68
Education (years)		10.4	10.0	3-16
Symptoms of psychosis (PANSS)				
Positive		15.6 (5.7)	15.0	7-36
Negative		16.3 (5.8)	15.0	7-39
General		36.2 (8.2)	35.5	19-63
Factor 1[1]		33.5(10.2)	32.0	15-70
Factor 2[1]		18.6 (6.8)	17.0	9-42
Depressive symptoms (BDI)		14.3 (11.1)	12.0	0-52
Functioning				
SOFAS[2]		40.7 (11.4)	40.0	15-65
RFS[3]		11.8 (3.2)	11.0	5-21

Ethnicity		
White		50.2
Aboriginal		30.5
Black		2.4
West Asian		.5
Other/unknown		9.5
Psychiatric diagnosis		
Schizophrenia	9.5	
Schizoaffective	4.8	
Major Depression	15.7	
Bipolar Disorder I	2.4	
Bipolar Disorder II	2.9	
Other psychoses	14.3	
Substance induced disorders	25.2	
Average days of substance use		
Alcohol		3.56 (6.85)
Cannabis		7.34 (10.03)
Powder cocaine		3.07 (6.93)
Crack cocaine		9.45 (10.02)
Methamphetamine		2.09 (5.06)
Heroin		4.17 (7.89)
Tobacco		24.09 (9.03)
Prescription Methadone		10.16 (13.45)
Substance Dependent Disorder		
Alcohol	18.1	
Cannabis	30.5	
Methamphetamine	24.8	
Powder cocaine	71.4	
Crack cocaine	67.1	
Heroin	39.0	
Traumatic brain injury (TBI)	6.2	
Viral infection		
HIV	16.7	
Hepatitis C (HCV)	70.0	
Hepatitis B (HBV)	37.3	
Herpes simplex (HSV)	89.5	
Cytomegalovirus (CMV)	71.9	
Liver Function		
Normal	78.1	
Hepatic Fibrosis	17.1	
Cirrhosis	4.8	

[1]Positive and Negative Syndrome Scale (PANSS) Factors specific to this sample were derived in a previous report (Giesbretch et al., 2016). Factor 1 = Psychosis/Disorganized symptoms; Factor 2 = Negative symptoms/Hostility
[2]Social and Occupational Functioning Scale total rating was used (full range: 0 - 100)
[3]Role Functioning Scale total rating was used (full range: 1 - 49)

1.1.2. Materials and Procedures

Independent variables.

Substance use. Substance use during the first five months of the study was measured monthly by trained research assistants using the Time Line Follow-Back (TLFB), a 10-minute interviewer administered method for obtaining quantitative estimates of drug use (Sobell & Sobell, 1982). The substances assessed include alcohol, cannabis, methamphetamine, heroin, powder cocaine, crack cocaine, and prescription methadone. Participants were asked to retrospectively estimate their drug use frequency in the past four weeks; answers can range from 0 to 28 days. The distributions of reported drug use were positively skewed and not amendable with data transformation. To improve the normality of distributions, we coded frequency of use into four groups. As shown in Table 2, for each substance, if a participant reported zero use in the first five months of the study, they were assigned a 0. The remaining participants were rank-ordered in terms of frequency of use. Lowest frequency users, representing the bottom one third of days of use, were assigned a 1. Middle frequency users, representing the middle one third of days of use, were assigned a 2. High frequency users, representing the top one third of days of use, were assigned a 3.

Table 2. Substance Use Characteristics (N = 210)

Substance	**Mean days used over 5 months (Range)**							
	None (0)	n	Low (1)	n	Middle (2)	n	High (3)	n
Alcohol	0	78	.33 (.2 - .7)	41	1.86 (.8 - 4.0)	48	15.0 (4.3 - 28.0)	43
Cannabis	0	84	1.37 (.2 - 3.6)	43	9.77 (3.8 – 18.0)	38	24.73 (18.2 – 28.0)	45
Heroin	0	123	1.30 (.2 -3.0)	29	7.22 (3.2-12.0)	31	22.74 (12.4 - 28.0)	27
MA	0	147	.80 (.2 – 1.6)	23	5.80 (2.0 – 10.2)	23	16.98 (11.4 – 28.0)	17
Powder cocaine	0	138	.62 (.2 - 1.5)	24	5.18 (1.8 - 11.2)	23	20.42 (11.6 - 28.0)	25
Crack cocaine	0	59	2.30 (.2 - 5.0)	44	10.64 (5.4 -17.0)	52	24.16 (17.2 - 28.0)	55
Prescription methadone	0	122	17.14 (1.2 - 24.7)	33	27.68 (25.4 - 28.0)	55		

The TLFB has been found to have good validity, showing moderate correlations with other measures of alcohol and substance use frequency (r = .39-.51) as well as high agreement with informant reports of drug use (r = .72-.91). The TLFB also demonstrates high test-retest

reliability for all substances (*r* = .73-.95; Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000). Further, self-reported substance use data was verified with urine drug testing in a subset of participants (n = 270; kappa = .66 - .70; Jones et al., 2013).

Psychiatric diagnoses. At baseline, all available clinical information was used to make DSM-IV-TR (American Psychiatric Association, 2000) psychiatric diagnoses, using procedures from the Best Estimate Clinical Evaluation and Diagnosis form (Endicott, 1988; Vila-Rodriguez et al., 2013). Reliability was previously established by examining independent diagnoses made by two psychiatrists for 98 participants, which yielded an acceptable kappa value of 0.77 for diagnoses of psychotic disorders and .60 for diagnoses of mood disorders (Vila-Rodriguez et al., 2013; Leckman, Sholomskas, Thompson, Belanger, & Weissman, 2012). We examined diagnoses of psychotic disorders (i.e., schizophrenia, schizoaffective disorder, psychotic disorder not otherwise specified (PNOS), depression with psychosis, and bipolar disorder with psychosis), depression, and bipolar disorder. Variables were coded dichotomously reflecting presence or absence of a diagnosis.

Viral infections. HIV exposure was identified using antibody detection. Positive serology is used to indicate Hepatitis C virus (HCV) and cytomegalovirus (CMV) exposure, while viral DNA detection by qPCR signifies HCV infection. Exposure to Hepatitis B virus (HBV) was identified using core antibody detection. Infection status was coded as a categorical variable indicating absence or presence of viral infection or exposure. Likelihood of hepatic fibrosis and cirrhosis, indicative of poorer liver functioning, was determined using the surrogate serological measure aspartate aminotransferase-to-Platelet Ratio Index (APRI; Wai et al., 2003). Values less than .7 indicate normal liver functioning, while values between .7 and 2.0 are associated with hepatic fibrosis, and values greater than 2.0 suggest hepatic cirrhosis.

Traumatic brain injury. All scans were acquired on a Phillips 3.0-T Achieva scanner (Phillips Healthcare, Amsterdam). High-resolution T1-weighted structural images, susceptibility-weighted images and standard clinical T2-weighted fluid attenuated images were evaluated for the presences of TBI. MRI evidence of TBI was coded as presence versus absence. Scanning protocols are available upon request.

Mediating variables.

Neurocognition. At baseline, trained research assistants administered neuropsychological tests of verbal memory, attention, response inhibition, and decision-making. As we sought to examine the role of global neurocognitive ability in predicting functioning for a range of diverse illnesses, we used a composite neurocognitive score, consisting of tests that were most highly correlated with one another (r = .37 - .43, p < .001). The raw scores for individual neurocognitive tests were converted into test-specific z-scores, and then these z-scores were summed and standardized into a composite z-score, reflecting overall neuropsychological performance. Test administrator validity ratings for all tests were reviewed to ensure that only valid data was analyzed; reasons for exclusion included excessive fatigue or poor engagement in testing, technical complications with computerized tasks, and early discontinuation from the task.

Response inhibition. The Stroop Interference Test consists of three components, where the participant must firstly name a series of color words, secondly name the color of a row of X's, and thirdly, on the Color-Word task, participants are presented with names of colors that are printed in a color different from the word itself and must name the color of the ink, not the actual word. The Stroop shows adequate test-retest reliability (r = .55-.92; Franzen, Tishelman, Sharp, & Friedman, 1987). The total of number of colors correctly named in a 45-second time period in the Color-Word task was used as a measure of response inhibition (Spreen & Strauss, 1998).

Memory. Verbal memory was assessed using the sum of the delayed recall scores of the Hopkins Verbal Learning Test Revised (HVLT-R; Brandt & Benedict, 2001). The HVLT-R consists of three immediate recall trials, where participants are read a list of 12 words and asked to recall as many words as possible following each of the three trials, and one delayed recall trial after approximately 20 minutes, where they are asked to recall as many words from the previously heard list as possible. The HVLT has demonstrated adequate reliability (r = .55-.78 for immediate recall scores; Benedict, Schretlen, Groninger, & Brandt, 1998) and validity, as it correlates highly with other measures of verbal memory (r = .75; Shapiro, Benedict, Schretlen, & Brandt, 1999).

Attention. Sustained attention was measured using the signal detection (A prime) score from the Rapid Visual Information Processing (RVIP), a subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996) where participants view a series of digits on a screen and are required to press a button in response to target sequences of digits (Sahakian & Owen, 1992). The A prime score is a measure of sensitivity to the target sequences. The RVIP has shown good test-retest correlations (r = .76-.80; Lowe & Rabbitt, 1998) and modest correlation with a composite measure of executive function/processing speed (r = .35; Smith et al., 2013).

Psychiatric symptoms. The Positive and Negative Syndrome Scale (PANSS), is a 30-item clinician-administered instrument measuring positive, negative, and general psychopathology symptoms. At baseline, research assistants completed ratings following an interview and a mental status examination. The presence and severity of each symptom is rated along a 7-point scale ranging from absent (1) to extreme (7), for a range of 7-49 for the positive scale, negative scale, and general psychopathology scale. PANSS has demonstrated high inter-rater reliability (r = .78-.83) and good criterion-related validity (r = .77; Kay, Opler, & Lindenmayer, 1987). Our team previously validated the presence of a three-factor PANSS structure within this sample, consisting of the factors Psychosis/Disorganized (Factor 1), Negative Symptoms/Hostility (Factor 2), and Insight/Awareness (Factor 3; Giesbrecht et al., 2016). Factor 1 and Factor 2 were entered as mediators between psychiatric diagnosis and ratings of functioning at 6-months, due to prior evidence for their association with the SOFAS (Giesbrecht et al., 2016).

Outcome variables. Ratings with the Social and Occupational Functioning Assessment Scale (SOFAS, Goldman, Skodol, & Lave, 1992) and the Role Functioning Scale (RFS, Goodman, Sewell, Cooley, Leavitt, 1993) were made at 6-month follow-up. The SOFAS was originally reported in the DSM-IV-TR as a potential tool for clinicians to obtain an estimate of general functioning in many areas of everyday living (Goldman, Skodol, & Lave, 1992). The SOFAS measures adult social and occupational functioning, where the assigned ratings take into consideration limitations due to mental or physical illness. The rating scale that ranges from 1 (grossly impaired functioning) to 100 (superior functioning). A score of 90 suggests good functioning and occupational and social effectiveness; 70 suggests some difficulty in functioning but generally functioning well; 50 suggests serious impairment in social, occupational, or school

functioning; 30 suggests the inability to function in almost all areas (Goldman, Skodol, & Lave, 1992; 4th Ed., text revision; DSM-IV-TR; American Psychiatric Association, 2000). The SOFAS shows high inter-rater reliability (*r* = .94) and moderate concurrent validity with other established measures of functioning (*r* = -.37 – .47; Hilsenroth et al., 2000).

The RFS is a measure of adult functioning in four domains: work productivity, independent living and self-care, and immediate and extended social network relationships. The rating for each domain ranges from 1 (minimal level of role functioning) to 7 (optimal level of role functioning). The RFS demonstrates high test-retest reliability (*r* = .85-.92) and inter-rater reliability (*r* = .64-.82), as well good criterion and construct validity in terms of its ability to distinguish between clinical and non-clinical groups and associations with real world indices of functioning (*r* = .50-.59; Goodman, Sewell, Cooley, Leavitt, 1993).

The raw total scores from each measure were converted into z-scores, which were summed. A final composite z-score was created from these summed scores, reflecting a composite score of functioning that equally weighted the SOFAS and RFS. Values below zero represent poorer functioning compared to the sample average, whereas values above zero indicate better functioning compared to the average. Trained and experienced research assistants who knew participants for a minimum of six months completed ratings with the SOFAS and RFS. Prior to assigning ratings, research assistants conducted an interview with the participant, and consulted other available clinical information. Research assistants who completed these ratings of functioning were not involved in neurocognitive testing and had no information about participants' neurocognitive performance.

1.1.3. Statistical Analysis

Demographic variables. We controlled for participant age, gender, and education in all mediation analyses.

Variable screening. To determine which illnesses were most strongly related to ratings of everyday and social functioning, Pearson product-moment and point biserial correlations were calculated between the independent variables (e.g., substance use, psychiatric illness, TBI) and the functional outcome score. Independent variables showing a

correlation coefficient greater than or equal to .12 were used in mediation analyses, corresponding to a small effect on functioning.

Mediation analyses. We used the PROCESS macro for mediation, a widely used add-on tool (Hayes, 2013). Following the recommended practice for testing multiple independent variables (Hayes, 2013), one mediation analysis was run for each independent variable, with the other independent variables and demographic variables entered as covariates. The neurocognitive composite score was entered as the mediator variable for all analyses. For independent variables related to psychiatric illness, PANSS Factors 1 (Psychosis/Disorganized) and 2 (Negative Symptoms/Hostility) were entered as parallel mediator variables alongside the neurocognitive composite score.

The primary interest of mediation is to estimate and interpret indirect and direct effects. The indirect effect (*ab*) is a measure of the amount of mediation. It is the product of *a*, which quantifies how much two participants who differ on one unit of the independent variable are estimated to differ on the mediating variable, and *b*, which quantifies how much two participants who are equal on the independent variable but differ on one unit of the mediating variable are estimated to differ on the outcome variable. The product, *ab*, indicates that when two cases differing by one unit on the independent variable, they are estimated to differ by *ab* units on the outcome variable as a result of the effect of the independent variable on the mediating variable. The direct effect (c') reflects the association between the independent and outcome variable when the indirect or mediated effect is controlled for. The total effect (c) is the sum of the direct and indirect effects.

We tested the mediation model using the bootstrapping procedure to estimate 95% confidence intervals. The bootstrapping procedure was chosen because it does not carry the assumption of normality of the sampling distribution of indirect effects, and has higher power than other tests, such as the Sobel test (Hayes, 2013). The bootstrap confidence interval is the recommended method for inference about the indirect effect in mediation analyses (Fritz & MacKinnon, 2007). Mediation is established if the 95% confidence intervals for the indirect effect does not include zero. Missing data resulted in listwise deletion. Additional details pertaining to the statistical procedures can be found in Appendix C.

Power. The bootstrap method is the most powerful test for testing the mediation effect, compared to the Baron and Kenny causal-steps approach (1986) and the Sobel test (Fritz & MacKinnon, 2007). With a sample size of 210, this study is able to detect small to medium sized mediation effects with a .80 probability (Fritz & MacKinnon, 2007).

Results

1.1.4. Correlations with functioning in the whole sample

Pearson product moment and point biserial correlations were calculated between the health characteristics and ratings of functioning at 6-months (see Table 3 for all coefficients). Heroin (r = -.13, p = .03) and methamphetamine (r = -.16, p = .01) use met our criterion for association with ratings of functioning. A diagnosis of a schizophrenia spectrum disorder was the only psychiatric illness to show an association with ratings of functioning meeting our criterion (r_{pb} = -.25, p < .01). MRI-defined TBI also showed such an association with the outcome variable (r_{pb} = -.12, p = .06). Viral infection did not a relationship to ratings of functioning that met our criterion, and neither did liver functioning status. Additional correlations regarding substance use, viral infection, and variables included in the mediation analysis can be found in Appendix A.

Table 3. Correlations between Illnesses and Functioning Score

Illness	Functioning z-score
Substance Use[a]	
Alcohol	.11
Cannabis	-.06
Powder cocaine	-.07
Crack cocaine	-.09
Methamphetamine	-.16
Heroin	-.13
Prescription methadone	.04
Psychiatric diagnosis[b]	
Schizophrenia/schizoaffective	-.25
Major Depression	-.08
Bipolar Disorder I	.04
Bipolar Disorder II	.11
Other psychoses	.02
Viral infection[c]	
HIV	-.02
Hepatitis C (HCV) exposure	.02
Hepatitis C (HCV) active infection	-.003

Hepatitis B (HBV)	.08
Herpes simplex (HSV)	.10
Cytomegalovirus (CMV)	.02
Liver Function[d]	.07
MRI-defined TBI[e]	-.12

[A] n = 267
[B] n = 312
[C] n = 302
[D] n = 305
[E] n = 264

1.1.5. Direct and indirect effects of illnesses on functioning

Substance use

As seen in *Figure 1*, greater frequency of heroin use had a significant direct effect on poorer ratings of functioning at 6 months (c' = -.18, *p* = .002). This indicates that for each transition to a more frequent heroin-using group (i.e., moving from the Low Use group to Middle Use group), functioning decreases by .18 standard deviation (SD) units, independent of the effect of neurocognition. The bootstrap confidence interval for the indirect effect of cognition using 10,000 bootstrap samples included zero (-.008 to .04), indicating there is no evidence that neurocognition mediated the relationship between greater frequency of heroin use and poorer ratings of functioning. Paradoxically, an increase in heroin use frequency led to an increase of .06 SD units in the neuropsychological composite score. The total effect of greater frequency of heroin use on poorer ratings of functioning was significant (c = -.17, *p* = .02).

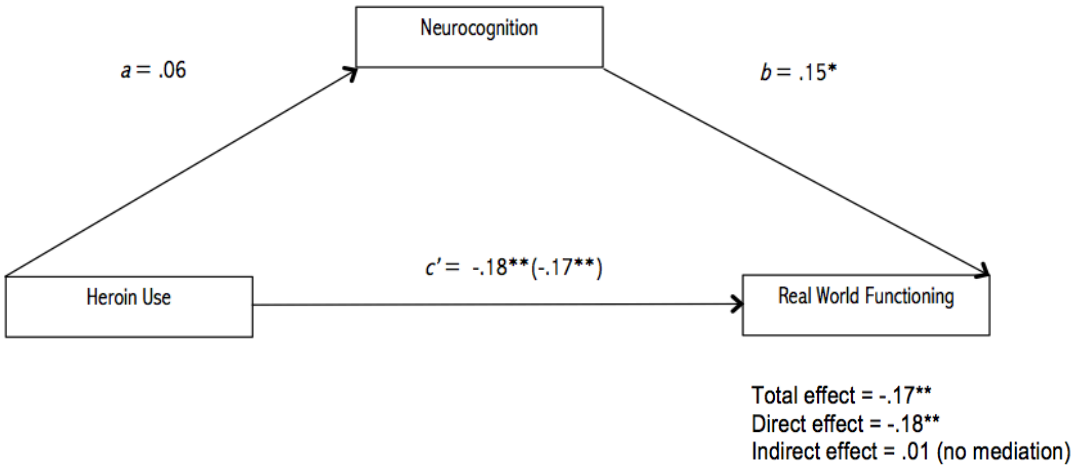

Figure 1. Model of the relationship between heroin use and real world functioning, and mediation of the relationship by neurocognition. Numbers are standardized regression coefficients. a*b indicates the indirect effect of neurocognition, c' indicates the direct effect of heroin use on functioning (i.e., excluding the effect of neurocognition), and the value in parentheses indicates the total effect. Note: *p < .05, **p < .01

As shown in *Figure 2*, greater frequency of methamphetamine use did not have a significant direct effect on poorer ratings of functioning at 6-months (c'= -.05, p = .17). The bootstrap confidence interval for the indirect effect of cognition using 10,000 bootstrap samples included zero (-.02 to .03), indicating that the neurocognitive composite score did not mediate the relationship between methamphetamine use and ratings of functioning. The total effect was thus non-significant as well (c = -.04, p = .19).

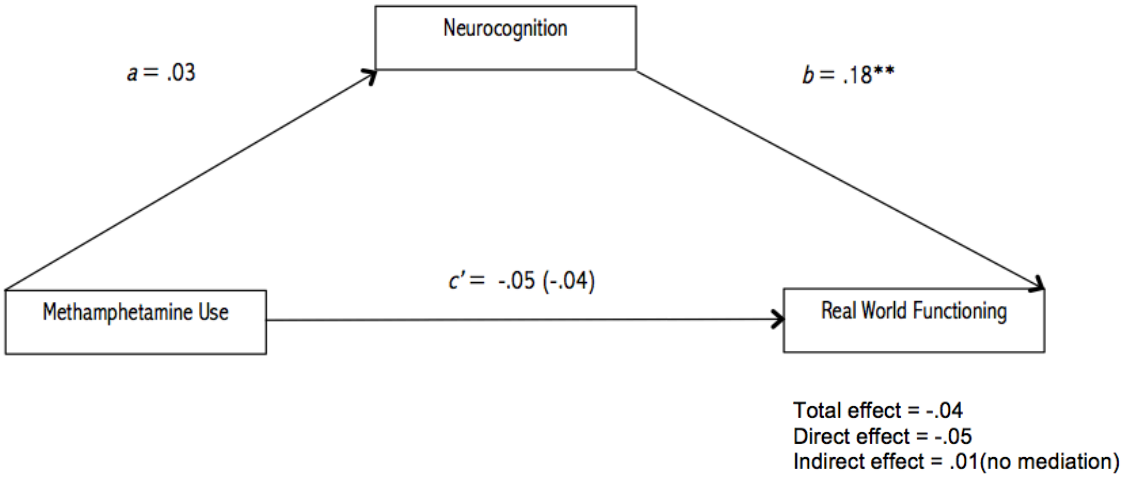

Figure 2. Model of the relationship between methamphetamine use and real world functioning, and mediation of this relationship by neurocognition. Numbers are standardized regression coefficients. *a*b* indicates the indirect effect of neurocognition, *c'* indicates the direct effect of methamphetamine use on functioning (i.e., excluding the effect of neurocognition), and values in parentheses indicate the total effect. Note: *p < .05, **p < .01

Psychiatric illness

As shown in *Figure 3*, schizophrenia did not have a significant direct effect on poorer ratings of functioning at 6 months (c' = -.30, p = .14). Instead, this relationship was significantly mediated by worse neurocognitive performance and higher PANSS Factor 1 and 2 scores, which were entered as parallel mediators (*ab* = -.27); the bootstrap confidence interval for the indirect effect, based on 10,000 bootstrap samples, was entirely below zero (-.50 to -.08). The value of the indirect effect indicated that having schizophrenia resulted in a .27 SD unit decrease in the functional outcome, as a result of the mediating effects of neurocognition and psychiatric symptoms. There was a significant total effect between having a diagnosis and poorer ratings of functioning (c = -.57, p = .002), with neurocognition and psychiatric symptoms accounting for 47.40% of this effect (-.27 / -.57).

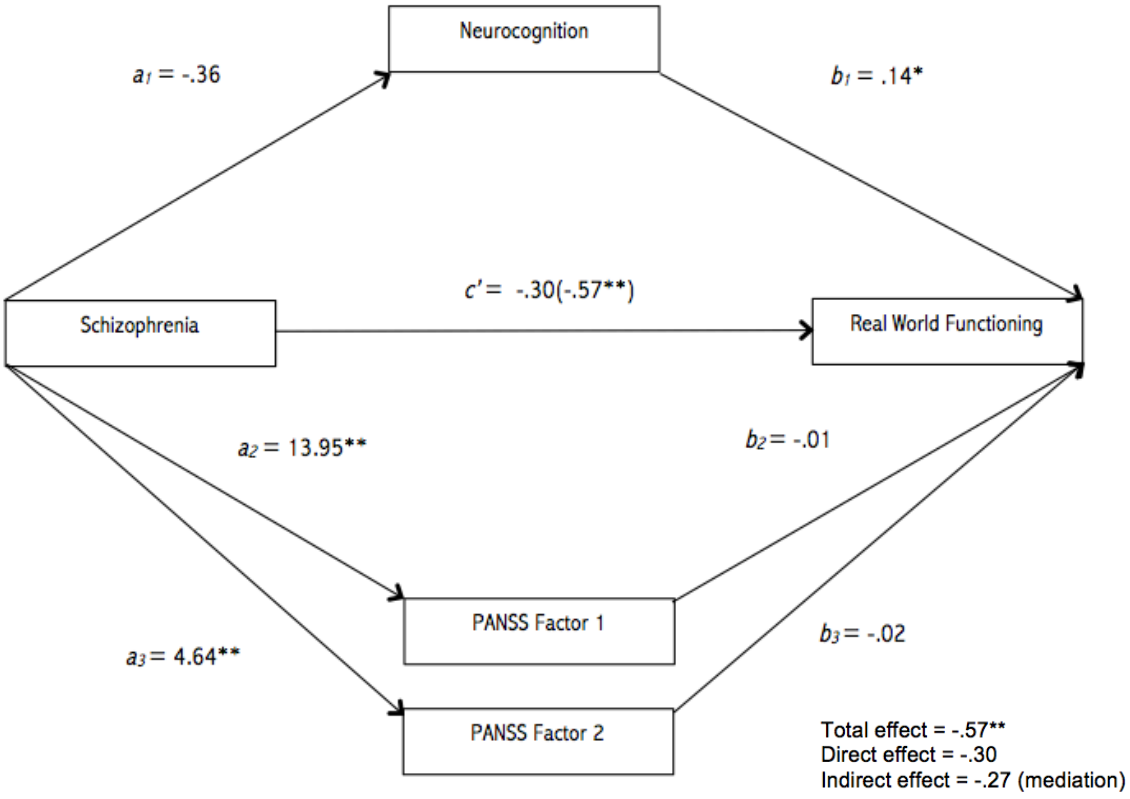

Figure 3. Model of the relationships between a schizophrenia diagnosis and real world functioning, and mediation of this relationship by neurocognition and PANSS Factors 1 and 2. Numbers are standardized regression coefficients. a*b indicates the specific indirect effects of neurocognition, PANSS Factor 1, and PANSS Factor 2. c' indicates the direct effect of schizophrenia on functioning (i.e., excluding the effects of neurocognition and PANSS factors), and values in parentheses indicate the total effect. Note: *p < .05, **p < .01

Tests of differences between the specific indirect effects of the different mediators indicated that neurocognition and the PANSS factors did not significantly differ from each other in their strength of mediating the relationship (i.e., all confidence intervals for individual effects included zero). The indirect/mediated effect on functioning for neurocognition was -.052, for PANSS Factor 1 (Psychotic/Disorganized) was -.132, and for PANSS Factor 2 (Negative Symptoms/Hostility) was -.087.

Traumatic Brain Injury

Figure 4 shows that traumatic brain injury (TBI) had a significant direct effect to poorer ratings of functioning at 6-months (c' = -.60, p = .01), meaning that those with TBI had a -.60 SD unit decrease in functioning independent of the mediating effect of neurocognition. Poorer neurocognition also mediated the relationship between MRI-defined TBI and poorer ratings of functioning (*ab* = -.08); bootstrap confidence interval for the indirect effect of cognition using 10,000 bootstrap samples was entirely below zero (-.24 to -.004). The indirect effect indicates that the presence of TBI is associated with a decrease of .08 SD units in functioning due to the mediating effect of neurocognition. Accordingly, the total effect between having MRI-defined TBI and poorer ratings of functioning was also significant (c = -.70, p = .01). Neurocognition therefore accounted for approximately 11% of the relationship between MRI-defined TBI and poorer ratings of functioning at 6 months (-.08 / -.70). Depression had virtually no association with TBI in this sample and was ruled out as potentially being able to explain the relationship between TBI and functioning (r = .005, p = .93)

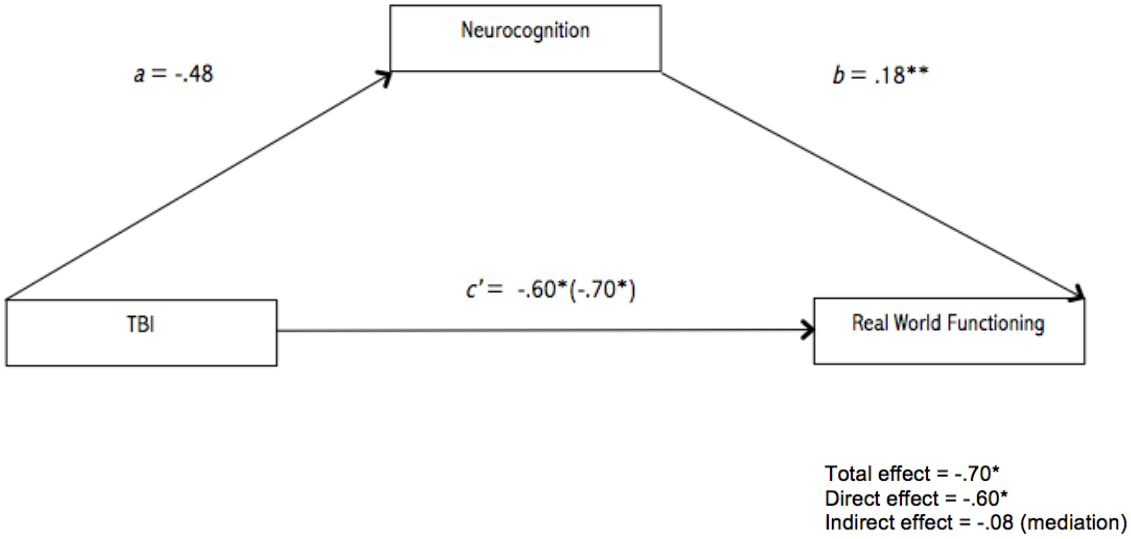

Figure 4. Model of the relationships among traumatic brain injury (TBI) and real world functioning, and mediation of this relationship by neurocognition. Numbers are standardized regression coefficients. *ab* indicates the indirect effect of neurocognition, *c'* indicates the direct effect of TBI on functioning (i.e., excluding the effect of neurocognition), and values in parentheses indicate the total effect. Note: *p < .05, **p < .0

Discussion

Multimorbid illness is prevalent in marginally housed populations (Koegel, Sullivan, Burnam, Morton, & Wenzel, 1999; Shannon, Ishida, Lai, & Tyndall, 2006; Fazel, Kohsla, Doll, & Geddes, 2008; Vila-Rodriguez et al., 2012). The present study identified health issues associated with everyday and social functioning at 6-month follow-up. Further, neurocognition and psychiatric symptoms selectively mediated these relationships. Results indicated that heroin use was negatively associated with functioning independent of effects on neurocognition, that neurocognition and positive and negative symptoms largely explained the impact of a schizophrenia diagnosis on poorer functioning, and that neurocognition partially mediated the effect of TBI on poorer functioning.

Key findings for substance use revealed that greater heroin use had a significant direct effect on poorer ratings of functioning. For each increase in coded heroin use frequency (e.g., going from group 0 to group 1), functioning is associated with a .18 standard deviation (SD) unit decrease, independent of the effects of neurocognition. This result demonstrates that even in the face of severe polysubstance use prevalent in marginally housed populations, on-going heroin use may be particularly detrimental to real world functioning. While it was hypothesized that stimulant use would similarly impair real world functioning, key differences in the behavioral effects of opiates versus stimulants likely explain the selective role of heroin use in impairing functioning within this sample. This finding is in line with past research on psychological and behavioral differences between persons who use opiates or stimulants more frequently. In stark contrast to the energizing properties of stimulant use, which helps users to overcome fatigue, and increase feelings of assertiveness, self-esteem, and hyperactivity, opiate use is associated with tranquilizing, calming, and dampening effects. Opiate use is typically associated with the urge to isolate or withdraw, and results in a much different behavioral profile than stimulant use, which motivates the user to more actively engage with the environment (Khantzian, 1985). Furthermore, those who use exclusively stimulants, compared to opiate-only users, have been found to have fewer drug-related problems, spend less money on drugs, and be less likely to enter substance abuse treatment (John et al., 2001).

Fundamental differences in the behavioral effects of opiate versus stimulant use are observed in animal studies; cocaine exposure in rats is associated with an approach-avoidance conflict towards drug injection sites and days of decreased drug intake, while opiate use is associated with a purely appetitive state that encourages only approach behaviors and consistently increased drug intake (Badiani, Belin, Epstien, Calu, & Shaham, 2011). Many characteristics specific to more frequent heroin use, such as prolonged periods of lethargy and drowsiness and a lack of averseness to drug taking, may play a role in these participants' poorer functional outcomes. These results suggest that within this marginally housed population, methamphetamine and cocaine use may have more limited associations to everyday functioning when heroin use and other health characteristics are taken into account. Whereas past research implicating methamphetamine and cocaine use in poorer real world outcomes has exclusively examined non-marginally housed samples (Weber et al., 2012; Preller et al., 2014ab), it may be valuable to examine the relative contributions of different types of substance use when considering functioning in a multimorbid sample. Finally, we observed null results for prescription methadone use on everyday functioning. As we did not specifically aim to examine the efficacy of methadone in this sample, it is premature to conclude that methadone did not impact functioning; further examination of more specific health and functional outcomes within predominant heroin users is needed.

Somewhat paradoxically, greater heroin use was associated with better neurocognitive performance; mediation analyses showed that by taking neurocognition into account, the strength of the association between greater frequency of heroin use and lower ratings of functioning actually decreased. Other studies have similarly reported that opioid dependency was associated with better performance in some cognitive domains (Baldacchino, Balfour, Passetti, Humphris, & Matthews, 2012). A study of marginally housed persons found that ethnic minority participants with substance dependence had a better neurocognitive composite score, with the authors suggesting that certain cognitive skills may be needed to acquire illicit substances (Stergiopoulos et al., 2015). Current opiate users also showed less cognitive impairment compared to other groups of substance users (Ersche, Clark, London, Robbins, & Sahakian, 2006). In sum, a relationship between opiate use and better neurocognitive performance is similar to what has been found in this study has been reported in the literature.

In line with our hypothesis regarding psychiatric illness, neurocognition and the PANSS factors mediated a sizeable proportion (approximately 47%) of the relationship between

schizophrenia and poorer ratings of functioning. The indirect effect showed that having schizophrenia resulted in a .27 SD unit decrease in the functional outcome, via the mediating effects of neurocognition and psychiatric symptoms. Infact, after controlling for this effect of mediation the direct relationship between schizophrenia and poorer functioning became non-significant. This finding is the first to reveal that in a sample of impoverished persons with schizophrenia living in socially marginalized housing, the pathways through which schizophrenic illness impair real world functioning are similar to what is seen in inpatient and outpatient samples (Ventura et al., 2008; Bowie et al., 2008; Leifker et al., 2009).

Comparisons of the mediated effects of neurocognition, and PANSS Factor 1 and 2 showed that they did not significantly differ from one another in their strength as mediators between schizophrenia and poorer functioning; only the total effect of these three variables yielded a significant effect of mediation. However, the magnitude of the indirect effect of PANSS Factor 1 (Psychotic/Disorganized; *ab* = -.13) was larger than the indirect effects of both neurocognition (*ab* = -.05) and PANSS Factor 2 (Negative Symptoms/Hostility; *ab* = -.09). Though previous schizophrenia research has mainly implicated negative symptoms and cognitive impairment in functional outcomes (Green, 1996), this finding indicates that there may be a more sizeable role for positive and disorganized symptoms in marginally housed adults with schizophrenia. Correspondingly, more recent studies have found associations between psychotic symptoms and real world functioning; employment outcome was negatively impacted by severity of psychotic symptoms in persons with schizophrenia in a supported employment program (McGurk et al., 2003), and Leifker et al. (2009) showed that positive symptoms such as hallucinatory behavior and suspiciousness predicted everyday outcome.

The distinctive social environment in which these persons with schizophrenia reside may mean that positive and disorganized symptoms associated with uncontrolled psychosis impair real world functioning to a larger degree than negative symptoms and neurocognitive impairment, in comparison to those residing in a more stable living situation. Whereas participants typically receive antipsychotic treatment in studies of inpatient and outpatient adults with schizophrenia, the current study highlights the need for superior treatment of positive symptoms in marginally housed persons with schizophrenia, who are an especially vulnerable sector of this population. We previously reported that less than a third of individuals in this sample with a psychotic disorder were treated with antipsychotic medication at baseline, and that for persons younger than 55, psychosis was significantly associated with earlier death

(Jones et al., 2016). Increased risk of mortality may be the preventable endpoint of the sequelae that follows from developing psychotic illness and consequent worse functioning in day-to-day living.

As hypothesized, the presence of MRI-defined TBI was associated with lower follow-up ratings of functioning; a significant direct effect showed that TBI resulted in .60 SD unit decrease in functioning independent of the mediating effect of neurocognition. Further, worse neurocognition mediated approximately 11% of the total relationship, with a significant indirect effect showing that TBI is associated with a decrease of .08 SD units in functioning as a result of poorer neurocognition. This is in line with research showing the large impact of moderate/severe TBI on cognitive impairment (Schretlena & Shapiroa, 2009). The direct relationship between TBI and poorer ratings of functioning remained significant even after neurocognition was accounted for, indicating that other factors associated with TBI may also be important when considering functioning. Hellawell, Taylor, & Pentland (2009) found that relatives reported family members with TBI to have similar amounts of functional problems, despite that those with more severe head injuries had greater cognitive impairment. A review of long-term outcomes in TBI showed that though better neurocognition was linked to greater independent living, self-reported psychological symptoms were more highly related to functioning in areas such as vocational ability, and family and other social relationships (Hoofien, Gilboa, Vakil, & Donovick, 2001). While depression was not linked to TBI in the current study, other psychological factors such as hostility, somatization, and anxiety may play a role in the effect of TBI on real world function. The relationship between TBI and real world outcomes is complex and there are likely many factors that contribute to an individual's ability to adapt to changes in the environment associated with having a brain injury, particularly in the unique social housing environments in which our participants reside.

Positive viral infection status for HIV, HCV, CMV, and HSV were not found to be associated with poorer ratings of functioning, and there were also null findings for the effect of hepatic fibrosis on functioning. There are a number of reasons that we observed these findings. Within this sample, the rate of HIV treatment (62%) is higher than treatment for both opiate dependence (50%) and psychosis (33%) (Vila-Rodriguez et al., 2013). As HIV-infected participants become more consistently treated with antiretroviral medication, their quality of life and activities of daily living are apt to be better preserved compared to those not receiving appropriate medical interventions for their illness. No associations were found between ratings

of functioning and HCV, HSV, and CMV infections likely because those with acute infections are often asymptomatic or show mild illness (e.g., fatigue, fever; WHO, 2016; Centre for Disease Control, 2016) compared to the severe illnesses (e.g., substance dependence, psychosis) that are more prominent within a marginally housed sample. Regarding the lack of association between liver functioning status and poorer functional outcome, hepatic fibrosis itself is not associated with additional symptoms apart from those developed in the existing course of HCV or HBV. In severe cases fibrosis may progress into cirrhosis, where the majority of liver tissue becomes scarred and unable to carry out its function. Cirrhosis is associated with symptoms such as abdominal swelling, variceal bleeding, and portosystemic encephalopathy (Bataller & Brenner, 2005). We may have been unable to observe an association between liver functioning status and poorer ratings of everyday functioning because only 5% of the sample showed evidence of cirrhosis. Overall, the effects of viral infections and/or hepatic fibrosis on everyday functioning may have been relatively small when other morbidities within this sample are also taken in to account, and the low prevalence of cirrhosis in the sample may have made it difficult to detect an effect.

Importantly, the present study demonstrates that neurocognition is an important pathway through which select health issues diminish everyday functioning in a multimorbid and marginally housed sample. Schutt et al. (2007) reported that better neurocognitive function at baseline predicted improved self-care and more positive social contacts in homeless persons with serious mental illness who had received housing. Another study found that homeless mentally ill persons provided with housing showed a significant improvement in neuropsychological functioning at 18-month follow-up, independent of changes in substance use, medication dosage or adherence, or time devoted to mental health services (Seidman et al., 2003). Because neurocognition represents a intermediary junction from illness to functional abilities and other research has shown neurocognition to be amenable to improvement with housing or stabilization interventions, such programs could directly influence neurocognitive ability and result in beneficial changes to everyday functioning and overall quality of life in marginally housed persons.

Some limitations in the present study should be considered. First, there is opportunity for error in the measurement of the outcome variable. Though ratings of functioning from research assistants who are highly familiar with the participants are used, the amount of convergence of these ratings with objective data or with other informant reports is unknown. However, past

investigations of real world functioning are subject to similar restrictions as they have also used rating scale assessments given by experienced research assistants, as well as participant self-report rating scales (Milev, Ho, Arndt, & Andresen, 2005; Temkin et al., 2009). Secondly, substance use information is obtained via self-report, and factors such as poor memory or impression management may impact the validity and reliability of these values. However, our research group has found strong associations between self-reported substance use data and urine drug analysis results (Jones et al., 2013). Thirdly, our neurocognitive test battery did not have multiple measures of specific neurocognitive domains, precluding the possibility of linking specific neurocognitive abilities to each of the individual illnesses. As our aim was to investigate the role of global neurocognition in mediating several illnesses on functioning in sample with complex health issues, a composite neurocognitive score served our purposes well, but future studies may move towards from examining more specific links between illnesses and certain neurocognitive abilities. Lastly, neurocognitive performance and illnesses were both measured at baseline. The cross-sectional nature of the data precludes determining whether premorbid neurocognition in some persons contributed to the subsequent development of health problems (e.g., participants with worse premorbid cognitive ability may have been more likely to engage in substance abuse or activities resulting in a head injury or viral infection). Despite this, literature on the emergence of select cognitive deficits only after illnesses have developed supports the model used in this study, which places neurocognition as an intermediary variable between illness and functioning. Research in various domains has also used similar models in predicting everyday function with cross-sectional data (e.g., Bowie et al., 2008; Heaton et al., 2002). Future research should also aim to develop and evaluate interventions targeting multimorbid illness in marginally housed and homeless populations. Determining whether comprehensive treatment strategies addressing multiple illnesses have an advantage over more traditional programs will provide valuable insight into the type of healthcare strategies that are needed to improve the health of this vulnerable population.

References

Baldacchino, A., Balfour, D. J. K., Passetti, F., Humphris, G., & Matthews, K. (2012). Neuropsychological consequences of chronic opioid use: a quantitative review and meta-analysis. *Neuroscience and Biobehavioral Reviews, 36*(9), 2056–68. http://doi.org/10.1016/j.neubiorev.2012.06.006

BC Ministry. (1994). *Nowhere to live: SROs: neither adequate not affordable*. *A call to action by the lower income urban singles task force*. Vancouver: British Columbia Ministry of Housing and Recreation Services.

Benedict, R. H. B., Schretlen, D., Groninger, L., & Brandt, J. (1998). Hopkins Verbal Learning Test – Revised: Normative Data and Analysis of Inter-Form and Test-Retest Reliability. *The Clinical Neuropsychologist, 12*(1), 43–55. http://doi.org/10.1076/clin.12.1.43.1726

Bowie, C. R., Leung, W. W., Reichenberg, A., McClure, M. M., Patterson, T. L., Heaton, R. K., et al. (2008). Predicting schizophrenia patients' real-world behavior with specific neuropsychological and functional capacity measures. *Biological Psychiatry, 63*(5), 505-511. doi:S0006-3223(07)00506-9 [pii]

Bowie, C. R., Reichenberg, A., Patterson, T. L., Heaton, R. K., & Harvey, P. D. (2006). Determinants of real-world functional performance in schizophrenia subjects: Correlations with cognition, functional capacity, and symptoms. *The American Journal of Psychiatry, 163*(3), 418-425. doi:163/3/418 [pii]

Brandt, J., & Benedict, R. H. B. (2001). *Hopkins verbal learning test-revised: Professional manual.* Lutz, FL: Psychological Assessment Resources Inc.

Carbon, M., & Correll, C. U. (2014). Thinking and acting beyond the positive: The role of the cognitive and negative symptoms in schizophrenia. *CNS Spectrums, 19 Suppl 1*, 38-52; quiz 35-7, 53. doi:10.1017/S1092852914000601

Carey, K. B., Carey, M. P., Maisto, S. A., & Henson, J. M. (2004). Temporal stability of the timeline followback interview for alcohol and drug use with psychiatric outpatients. *Journal of Studies on Alcohol, 65*(6), 774-781.

Crane, N.A., Schuster, R.M., Fusar-Poli, P., Gonzalez, R. (2013). Effects of Cannabis on Neurocognitive Functioning: Recent Advances, Neurodevelopmental Influences, and Sex Differences. *Neuropsychological Review, 23*, 117-137. doi: 10.1007/s11065-012-9222-1

Crean, R.D., Crane, N.A., & Mason, B.J. (2011). An Evidence Based Review of Acute and Long-Term Effects of Cannabis Use on Executive Cognitive Functions. *Journal of Addiction Medicine, 5*(1), 1-8. doi:10.1097/ADM.0b013e31820c23fa.

Dickerson, F., Stallings, C., Origoni, A., Katsafanas, E., Schweinfurth, L.A., Savage, C.L., & Yolken, R. (2014). Association between cytomegalovirus antibody levels and cognitive functioning in non-elderly adults. PLoS One, 9(5):e95510. doi: 10.1371/journal.pone.0095510.

Doyle, K.L., Morgan, E.E., Morris, S., Smith, D.M., Little, S., Iudicello, J.E., Blackstone, K., Moore, D.J., Grant, I., Letendre, S.L., Woods, S.P., & the Translational Methamphetamine AIDS Research Center (TMARC) Group. Real-world impact of neurocognitive deficits in acute and early HIV infection. *The Journal of NeuroVirology, 19*(6), 565-573. doi: 10.1007/s13365-013-0218-2

Endicott, J. (1988). *Best estimate clinical evaluation and diagnosis form (BECED)*. Department of Research Assessment and Training, New York State Psychiatric Institute, New York, NY.

Evans, J. D., Heaton, R. K., Paulsen, J. S., Palmer, B. W., Patterson, T., & Jeste, D. V. (2003). The relationship of neuropsychological abilities to specific domains of functional capacity in older schizophrenia patients. *Biological Psychiatry, 53*(5), 422-430. doi:S0006322302014762 [pii]

Fals-Stewart, W., O'Farrell, T. J., Freitas, T. T., McFarlin, S. K., & Rutigliano, P. (2000). The timeline followback reports of psychoactive substance use by drug-abusing patients: Psychometric properties. *Journal of Consulting and Clinical Psychology, 68*(1), 134-144.

Fazel, S., Khosla, V., Doll, H., & Geddes, J. (2008). The prevalence of mental disorders among the homeless in western countries: Systematic review and meta- regression analysis. *PLoS Medicine*, *5*(12), 1670-1681. doi:10.1371/journal.pmed.0050225

Fett, A. K., Viechtbauer, W., Dominguez, M. D., Penn, D. L., van Os, J., & Krabbendam, L. (2011). The relationship between neurocognition and social cognition with functional outcomes in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews, 35*(3), 573-588. doi:10.1016/j.neubiorev.2010.07.001 [doi]

Franzen, M.D., Tishelman, A.C., Sharp, B.H., & Friedman, A.G. (1987). An investigation of the test-retest reliability of the Stroop Color-Word Test across two intervals. *Archivals of Clinical Neuropsychology, 2*(3), 265-275.

Fray, P. J., Robbins, T. W., & Sahakian, B. J. (1996). Neuropsychiatric applications of CANTAB. *International Journal of Geriatric Psychiatry, 11*, 329-336.

Fray, P.J., Robbins, T.W., & Sahakian, B.J. (1996). Neuropsychiatric applications of CANTAB. *International Journal of Geriatric Psychology, 11*, 329-336.

Giesbrecht, C. J., O'Rourke, N., Leonova, O., Strehlau, V., Paquet, K., Vila-Rodriguez, F., et al. (2016). The Positive and Negative Syndrome Scale (PANSS): A Three-Factor Model of Psychopathology in Marginally Housed Persons with Substance Dependence and Psychiatric Illness. PLos One, 11(3), e0151648. doi: 10.1371/journal.pone.0151648

Goldberg, T., & Green, M. (2002). Neurocognitive functioning in patients with schizophrenia: an overview. In: Davis, K.L., Charney, D., Coyle, J.T., Nemeroff, C., editors. *Neuropsychopharmacology: The Fifth Generation of Progress* (657-669). Philadelphia, PA: Williams & Wilkins, Lippincott.

Goldman, H. H., Skodol, A. E., & Lave, T. R. (1992). Revising axis V for DSM-IV: A review of measures of social functioning. *The American Journal of Psychiatry, 149*(9), 1148-1156. doi:10.1176/ajp.149.9.1148 [doi]

Goodman, S. H., Sewell, D. R., Cooley, E. L., & Leavitt, N. (1993). Assessing levels of adaptive functioning: The role functioning scale. *Community Mental Health Journal, 29*(2), 119-131.

Gorman, A.A., Foley, J.M., Ettenhofer, M.L., Hinkin, C.H., & van Gorp, W.G. (2009). Functional consequences of HIV-associated neuropsychological impairment. *Neuropsychological Review, 19*(2), 186-203. doi: 10.1007/s11065-009-9095-0

Green, M.F., Kern, R.S., Heaton, R.K. (2004). Longitudinal studies of cognition and functional outcome in schizophrenia: implications for MATRICS. *Schizophrenia Research, 72*(1), 41-51.

Harvey, P. D., Howanitz, E., Parrella, M., White, L., Davidson, M., Mohs, R. C., et al. (1998). Symptoms, cognitive functioning, and adaptive skills in geriatric patients with lifelong schizophrenia: A comparison across treatment sites. The American Journal of Psychiatry, 155(8), 1080-1086. doi:10.1176/ajp.155.8.1080 [doi]

Hayes, A. (2013). *Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-Based Approach.* New York, NY: The Guildford Press.

Hilsenroth, M. J., Ackerman, S. J., Blagys, M. D., Baumann, B. D., Baity, M. R., Smith, S. R., et al. (2000). Reliability and validity of DSM-IV axis V. *The American Journal of Psychiatry, 157*(11), 1858-1863. doi:10.1176/appi.ajp.157.11.1858 [doi]

Jaeger, J., Berns, S., Uzelac, S., & Davis-Conway, S. (2006). Neurocognitive deficits and disability in major depressive disorder. *Psychiatry Research, 145*(1), 39-48.

Jones, A. A., Vila-Rodriguez, F., Leonova, O., Langheimer, V., Lang, D. J., Barr, A. M., et al. (2015). Mortality from treatable illnesses in marginally housed adults: A prospective cohort study. *BMJ Open, 5*(8), e008876-2015-008876. doi:10.1136/bmjopen-2015-008876 [doi]

Jones, A. A., Vila-Rodriguez, F., Panenka, W. J., Leonova, O., Strehlau, V., Lang, D. J., et al. (2013). Personalized risk assessment of drug-related harm is associated with health outcomes. *PloS One, 8*(11), e79754. doi:10.1371/journal.pone.0079754 [doi]

Jovanovski, D., Erb, S., & Zakzanis, K. K. (2005). Neurocognitive deficits in cocaine users: a quantitative review of the evidence. *Journal of Clinical and Experimental Neuropsychology, 27*(2), 189–204. http://doi.org/10.1080/13803390490515694

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261-276.

Koegel, P., Sullivan, G., Burnam, A., Morton, S. C., & Wenzel, S. (1999). Utilization of mental health and substance abuse services among homeless adults in los angeles. *Medical Care, 37*(3), 306-317.

Lasser, R. A., Nasrallah, H., Helldin, L., Peuskens, J., Kane, J., Docherty, J., et al. (2007). Remission in schizophrenia: Applying recent consensus criteria to refine the concept. *Schizophrenia Research, 96*(1-3), 223-231. doi:S0920-9964(07)00201-0 [pii]

Leckman, J. F., Sholomskas, D., Thompson, W. D., Belanger, A., & Weissman, M. M. (1982). Best estimate of lifetime psychiatric diagnosis: A methodological study. *Archives of General Psychiatry, 39*(8), 879-883.

Leckman, J.F., Sholomskas, D., Thompson, W.D., Belanger, A., & Weissman, M.M. (1982). Best estimate of lifetime psychiatric diagnosis: a methodological study. Archivals of General Psychiatry, 39(8), 879-883.

Leifker, F. R., Bowie, C. R., & Harvey, P. D. (2009). Determinants of everyday outcomes in schizophrenia: The influences of cognitive impairment, functional capacity, and symptoms. *Schizophrenia Research, 115*(1), 82-87. doi:10.1016/j.schres.2009.09.004 [doi]

Lieb, K., Engelbrecht, M.A., Gut, O., Fiebich, B.L., Bauer, J., Jans-sen, G., & Schaefer, M. (2006). Cognitive impairment in patients with chronic hepatitis treated with interferon alpha (IFNalpha): Results from a prospective study. *European Psychiatry, 21*(3), 204-210.

Lowe, C., & Rabbitt, P. (1998). Test/re-test reliability of the CANTAB and ISPOCD neuropsychological batteries: Theoretical and practical issues. *Neuropsychologia, 36*, 915–923. doi:10.1016/S0028-3932(98)00036-0

Mattick, R.P., Breen, C., Kimber, J., & Davoli, M. (2009). Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. *Cochrane Database of Systematic Reviews*, Jul 8;(*3*):CD002209. doi: 10.1002/14651858.CD002209.pub2

Milev, P., Ho, B. C., Arndt, S., & Andreasen, N. C. (2005). Predictive values of neurocognition and negative symptoms on functional outcome in schizophrenia: A longitudinal first-episode study with 7-year follow-up. *The American Journal of Psychiatry, 162*(3), 495-506. doi:162/3/495 [pii]

Nutt, D. J., King, L. A., Phillips, L. D., & Independent Scientific Committee on Drugs. (2010). Drug harms in the UK: A multicriteria decision analysis. *Lancet (London, England), 376*(9752), 1558-1565. doi:10.1016/S0140-6736(10)61462-6 [doi]

Preller, K. H., Herdener, M., Schilbach, L., Stampfli, P., Hulka, L. M., Vonmoos, M., & Quednow, B. B. (2014). Functional changes of the reward system underlie blunted response to social gaze in cocaine users. *Proceedings of the National Academy of Sciences*, *USA, 111*(7), 2842–2847.

Preller, K. H., Hulka, L. M., Vonmoos, M., Jenni, D., Baumgartner, M. R., Seifritz, E., Dziobek, I. and Quednow, B. B. (2014), Impaired emotional empathy and related social network deficits in cocaine users. *Addiction Biology, 19*, 452–466. doi: 10.1111/adb.12070

Rajji, T. K., Miranda, D., & Mulsant, B. H. (2014). Cognition, function, and disability in patients with schizophrenia: A review of longitudinal studies. *Canadian Journal of Psychiatry.Revue Canadienne De Psychiatrie, 59*(1), 13-17.

Reed, G.M., Spaulding, W. D., Bufka, L. F. (2009). The relevance of the International Classification of Functioning, Disability and Health (ICF) to mental disorders and their treatment. *The European Journal of Disability Research*, *3*(4), 340-359. doi: 10.1016/j.alter.2008.11.003

Rock, P.L., Roiser, J.P., Riedel, W.J., & Blackwell, A.D. (2014). Cognitive impairment in depression: a systematic review and meta-analysis. *Psychological Medicine, 44*(10), 2029-2040. doi: 10.1017/S0033291713002535

Sadek, J.R., Vigil, O., Grant, I., Heaton, R.K., & the HNRC Group. (2007). The impact of neuropsychological functioning and depressed mood on functional complaints in HIV-1 infection and methamphetamine dependence. Journal of Clinical and Experimental Neuropsychology, 29(3), 266-276.

Sahakian, B. J., & Owen, a M. (1992). Computerized assessment in neuropsychiatry using CANTAB: discussion paper. *Journal of the Royal Society of Medicine, 85*, 399-402.

Schuster, R.M., Crane, N.A., Mermelstein, R., & Gonzalez, R. (2012). The influence of inhibitory control and episodic memory on the risky sexual behavior of young adult cannabis users. *Journal of the International Neuropsychological Society, 18*(5), 827-33. doi: 10.1017/S1355617712000586

Shannon, K., Ishida, T., Lai, C., & Tyndall, M. W. (2006). The impact of unregulated single room occupancy hotels on the health status of illicit drug users in Vancouver. International Journal of Drug Policy, 17(2), 107-114. doi:10.1016/j.drugpo.2005.09.002

Smith, P. J., Need, A. C., Cirulli, E. T., Chiba-Falek, O., & Attix, D. K. (2013). A comparison of the Cambridge Automated Neuropsychological Test Battery (CANTAB) with "traditional" neuropsychological testing instruments. *Journal of Clinical and Experimental Neuropsychology, 35*(3), 319–28. http://doi.org/10.1080/13803395.2013.771618

Sobell, L. C., & Sobell, M. B. Timeline Follow Back user's guide: A calendar method for assessing alcohol and drug use. Toronto: Addiction Research Foundation; 1996.

Spreen, O., & Strauss, E. (1998). *A compendium of neuropsychological tests: Administration, norms, and commentary* (2nd ed.). NY: Oxford University Press.

Stavro, K., Pelletier, J., & Potvin, S. (2013). Widespread and sustained cognitive deficits in alcoholism: a meta-analysis. *Addiction Biology, 18*(2), 203–13. http://doi.org/10.1111/j.1369-1600.2011.00418.x

Strassnig, M. T., Raykov, T., O'Gorman, C., Bowie, C. R., Sabbag, S., Durand, D., et al. (2015). Determinants of different aspects of everyday outcome in schizophrenia: The roles of negative symptoms, cognition, and functional capacity. *Schizophrenia Research, 165*(1), 76-82. doi:10.1016/j.schres.2015.03.033 [doi]

The World Health Organization. (2002). Towards a Common Language for Functioning, Disability and Health: The International Classification of Functioning, Disability and Health.

Velligan, D. I., Mahurin, R. K., Diamond, P. L., Hazleton, B. C., Eckert, S. L., & Miller, A. L. (1997). The functional significance of symptomatology and cognitive function in schizophrenia. Schizophrenia Research, 25(1), 21-31. doi:S0920-9964(97)00010-8 [pii]

Ventura, J., Hellemann, G. S., Thames, A. D., Koellner, V., & Nuechterlein, K. H. (2009). Symptoms as mediators of the relationship between neurocognition and functional outcome in schizophrenia: A meta-analysis. *Schizophrenia Research, 113*(2-3), 189-199. doi:10.1016/j.schres.2009.03.035 [doi]

Vila-Rodriguez, F., Panenka, W. J., Lang, D. J., Thornton, A. E., Vertinsky, T., Wong, H., et al. (2013). The hotel study: Multimorbidity in a community sample living in marginal housing. *The American Journal of Psychiatry, 170*(12), 1413-1422. doi:10.1176/appi.ajp.2013.12111439 [doi]

Wai, C. T., Greenson, J. K., Fontana, R. J., et al. (2003). A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology, 38, 518–526.

Weber, E., Blackstone, K., Iudicello, J.E., Morgan, E.E., Grant, I., Moore, D.J., Woods, S.P., & The Translational Methamphetamine AIDS Research Center (TMARC) Group. (2012). Neurocognitive deficits are associated with unemployment in chronic methamphetamine users. *Drug and Alcohol Dependence, 125*(0), 146-153. doi:10.1016/j.drugalcdep.2012.04.002

Appendix A.

Additional Tables

Table 1 Pearson Product-moment Correlation Coefficients between Substances

		1	2	3	4	5	6	7	8	9
1.	**Functioning**	1								
2.	**Heroin**	-.13*	1							
3.	**Methamphetamine**	-.15*	.24**	1						
4.	**Alcohol**	.11	-.10	-.08	1					
5.	**Cannabis**	-.06	-.17**	.21*	.18*	1				
6.	**Powder cocaine**	-.07	.33**	-.03	.02	.03	1			
7.	**Crack cocaine**	.09	.17*	-.32**	-.03	-.12	.18**	1		
8.	**Amphetamines**	-.08	.15*	.22*	.08	.02	-.02	-.11	1	
9.	**Prescription methadone**	.04	.25*	.09	-.25*	-.14*	.14*	.09	.04	1

n=262
*p<.05, **p<.01

Table 2 Point Biserial Correlation Coefficients between Viral Infections

		1	2	3	4	5	6	7
1.	**Functioning**	1						
2.	**HIV**	-.02	1					
3.	**Hepatitis C**	-.00	.23**	1				
4.	**Hepatitis B**	.07	.21**	.41**	1			
5.	**CMV**	.01	.07	.00	.16**	1		
6.	**Herpes Simplex**	.10	-.01	.17**	.18**	.26**	1	
7.	**Liver function**	.08	.13	.26**	.09	-.04	.05	1

Note: HIV = Human Immunodeficiency Virus, CMV = Cytomegalovirus
n=342
*p<.05, **p<.01

Table 3 Pearson Product-moment and Point Biserial Correlation Coefficients between Variables Included in Mediation Analyses

	1	2	3	4	5	6	7	8
1. Functioning	1							
2. Heroin	-.13*	1						
3. Methamphetamine	-.15*	.24**	1					
4. Schizophrenia	-.25**	.11	-.09	1				
5. TBI	-.12	-.09	.00	-.05	1			
6. Age	.11	-.13*	-.30**	-.15**	.19**	1		
7. Gender	.07	.12*	.07	-.07	-.07	-.12	1	
8. Education	.05	-.007	-.02	.06	-.06	.07	-.07	1

Note: TBI= Traumatic Brain Injury
*p<.05, **p<.01

Table 4 Correlation Coefficients between Neurocognition and Other Variables

	Neurocognition
Functioning [a]	.14*
Substance Use [b]	
Heroin	.13*
Methamphetamine	.09
Alcohol	-.02
Cannabis	-.10
Powder cocaine	-.02
Crack cocaine	-.07
Prescription methadone	.03
Psychiatric illness and symptoms [c]	
Schizophrenia	-.03
Bipolar	.13*
Bipolar II	.05
Depression	-.10
Other psychoses	-.08
PANSS Factor 1 [d]	-.19**
PANSS Factor 2 [d]	-.15*
Viral infection [e]	

Cytomegalovirus	.01
Herpes Simplex Virus	-.06
Hepatitis B virus	-.11
Hepatitis C virus	-.11
HIV	-.11
Liver function [f]	-.05
Traumatic Brain Injury [g]	-.11

[A] n = 288
[B] n = 256
[C] n = 323
[D] n = 291
[E] n ranges 300 to 310
[F] n = 312
[G] n = 273
Note: *p < .05, **p < .01

Appendix B.

Missing Data

Table 4 Distribution of Missing Data Across Variables in Participants Excluded from Mediation Analysis

	Age	Sex	Edu	HER	MA	SZ	F1	F2	Cognition	Functioning	TBI
Valid	142	142	142	68	63	161	105	104	113	102	82
Missing	27	27	27	101	106	8	64	65	56	67	87

Note. Edu = Education, HER = Heroin use, MA = Methamphetamine use, SZ = Schizophrenia, F1 = Positive and Negative Syndrome Scale (PANSS) Factor 1, F2 = PANSS Factor 2, TBI = Traumatic brain injury

Appendix C.

Assumption Checking

Prior to running the mediation analyses, linearity of relationships between the independent and dependent variables were visually determined using scatterplots. Normality of continuous variables was assessed using tests of skewness and kurtosis. Multicollinearity was determined by examining tolerance and variance inflation factor values.