

Neurocognitive Profiles of Marginalized Persons with Comorbid Substance Dependence, Viral Infection, and Psychiatric Illness

by

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Abstract

Individuals living in single-room occupancy (SRO) hotels constitute a marginalized population with exposure to adverse risk factors, including substance use, viral infection, and psychiatric illness. The current study used cluster analysis to identify and describe subgroups of individuals with common profiles of neurocognitive functioning in 249 SRO residents. Results revealed three distinct subgroups. Cluster 1 (n = 59) presented as higher functioning, whereas Cluster 3 (n = 87) exhibited the lowest functioning with a relative strength in decision-making. Conversely, Cluster 2 (n = 103) was characterized by neurocognitive abilities that bisected the performance of the other groups, but with a relative weakness in decision-making. A discriminant function analysis revealed that the neurocognitive variables comprised two dimensions that accounted for between-group variance. Clusters meaningfully differed on several external variables. Overall, this study revealed that neurocognition provides the basis for identifying meaningful subgroups of individuals and may be informative to intervention strategies.

Keywords: cluster analysis; cognition; substance-related disorders; psychosis; dual diagnosis; substandard housing

For Omí and Papa

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Introduction

Individuals living in single-room occupancy hotels (SROs) constitute one of the most marginalized populations of society, and are considered by the United Nations as “at risk for homelessness”. In fact, many marginally housed persons have a history of homelessness, as well as transient, unstable housing (Robertson et al., 2004; Shannon, Ishida, Lai, & Tyndall, 2006). The living conditions of SRO residents are substandard, yet this remains a common housing solution for socially marginalized individuals. Substandard housing situations are a global issue and are on the rise in both developing and industrialized nations, contributing significantly to social and health inequities (Vlahov et al., 2007). Living in precarious conditions, this population faces numerous mental and physical health risks. Dwelling in an SRO has been found to be associated with HIV and Hepatitis C virus (HCV) infection, emergency room use, incarceration, physical assault, and severe drug use (Shannon, Ishida, Lai, & Tyndall, 2006). In some instances, the prevalence of HIV infection has been noted to be fivefold the regional norm (Robertson et al., 2004). Likewise, the lifetime prevalence of mental illness is high, with rates for psychosis and major depression upwards of 40% in homeless persons (Fazel, Kohsla, Doll, & Geddes, 2008). Prevalence rates for concurrent substance use and mental disorders in the homeless are notably higher (Koegel, Sullivan, Burnam, Morton, & Wenzel, 1999; Strehlau, Torchalla, Li, Schuetz, & Krausz, 2012). When compared to substance users with stable housing, the alcohol, drug, and mental health problems experienced by the homeless and marginally housed are of greater severity (Eyrich-Garg, Cacciola, Carise, Lynch, & McLellan, 2008). Other negative exposures of marginalized individuals include high rates of childhood trauma (Pluck et al., 2011; Torchalla, Strehlau, Li, Schuetz, & Krausz, 2012), frequent use of the hospital emergency room (Kushel, Perry, Bangsberg, Clark, & Moss, 2002), and an increased rate of food insecurity (Weiser et al., 2009). Not surprisingly, this population experiences poor outcomes. Marginalized persons with HIV infection are two to four times more likely to engage in health risk behaviours, including injection drug use and unprotected

sex (Aidala, Cross, Stall, Harre, & Sumartojo, 2005). These individuals are also likely to experience worse clinical outcomes from HIV infection, impaired social functioning, and poor perceived health-related quality of life (Weiser et al., 2009). Even after accounting for their low income, the marginally housed inevitably have significantly higher mortality rates than what would be expected (Hwang, Wilkins, Tjepkema, O'Campo, & Dunn, 2009). In Canada, remaining life expectancy for men is ten years less than that of the national cohort, and seven years less for women.

The various substance-related, viral, and psychiatric risks that marginalized persons routinely encounter across the lifespan may impose a substantial neuropsychological burden. Developmentally, childhood psychological trauma is associated with poor executive functioning and low IQ in homeless adults (Pluck et al., 2011). Furthermore, there are widespread cognitive consequences associated with alcohol and illicit drug abuse (Lundqvist, 2005; Yücel, Lubman, Solowij, & Brewer, 2007). Impairments tend to be worse in chronic substance abusers (Hanson, Cummins, Tapert, & Brown, 2011) and persist despite short-term abstinence (Block, Erwin, & Ghoneim, 2002). Moderate cognitive deficits have been noted in the symptomatic stage of HIV infection, while milder deficits are evident in the asymptomatic stage (Reger, Welsh, Razani, Martin, & Boone, 2002). Likewise, HCV infection is linked to cognitive impairments, despite clearance of the virus from the system (Forton, Taylor-Robinson, & Thomas, 2006; Weissenborn et al., 2009).

Regarding major mental illness, medium to large deficits across multiple cognitive domains have been consistently reported in schizophrenia. Impairments are apparent at the first episode of illness and appear to be relatively stable (Heinrichs & Zakzanis, 1998; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009). More modest deficits are also evident in other non-spectrum psychoses (Dickerson et al., 2011; Zanelli et al., 2010). Cognitive impairments have also been consistently reported in the euthymic phases of persons with major depression (Bhardwaj, Wilkinson, Srivastava, & Sharma, 2010; Hammar & Ardal, 2009) and bipolar disorder (Bora, Yücel, & Pantelis, 2009; Torres, Boudreau, & Yatham, 2007). Mild traumatic brain injury (TBI) is generally associated with mild and transient cognitive impairment, but substantial and enduring impairments emerge in persons with moderate to severe TBI (Schretlen & Shapiro, 2003) or in the context of multiple injuries and/or comorbidities (Carey et al.,

2006; Cherner et al., 2005; Letendre et al., 2005; Martin-Thoymeyer & Paul, 2009; Rippeth et al., 2004).

Altogether, marginalized persons encounter a multitude of shared risks factors that may damage or dysregulate the brain circuitry that subserves cognition. Each individual's exposure is apt to vary, as are their innate cognitive capacities. Nonetheless, subgroups of individuals with common neurocognitive profiles may be identifiable for two reasons. First, individuals who share aetiologies that dysregulate the same brain circuitry are apt to exhibit a similar neurocognitive profile of dysfunction. Second, equifinite processes may come into play, such that different external factors may insult brain circuitry in a similar fashion, leading to comparable profiles of functioning (e.g. Lange, Iverson, & Franzen, 2008). Characterizing the neurocognitive consequences of these individuals is apt to be of value because individual difference in neurocognition is associated with at least three core outcome domains, including clinical symptomatology (e.g. Dominguez, Viechtbauer, Simons, van Os, & Krabbendam, 2009; Margolin, Avants, Warburton, & Hawkins, 2002), health risk behaviours (e.g. Bousman et al., 2010; Ersche et al., 2005), and everyday functioning (e.g. Morgan & Heaton, 2009).

The aim of the current study is to use cluster analysis techniques to group SRO residents based on similar patterns of functioning across a range of cognitive domains, including premorbid IQ, verbal memory, attention, and executive functions. A second aim is to validate the derived clusters by examining whether meaningful differences exist between subgroups on putative risk factors of cognitive dysfunction and on core clinical and functional outcomes. Elucidating the common patterns of neurocognitive functioning and their associated features would be informative to intervention strategies. This is especially relevant because these elements are not addressed in terms of assessment or support in the current system, and serves to further limit the ability of these individuals to navigate a complex, high threshold system of care.

Consistent with existing literature, we anticipated a profile characterized by the lowest overall neurocognitive functioning to exhibit more severe symptoms of psychosis (Dominguez et al., 2009; Lindsberg, Poutiainen, & Kalska, 2009), increased depressive symptomatology (Hammar & Årdal, 2009), and the poorest social and role functioning (Morgan & Heaton, 2009). Given the vulnerability of frontal brain circuitry to various

risks (e.g. Murrrough, Iacoviello, Neumeister, Charney, & Iosifescu, 2011; Yücel et al., 2007), we also expected a profile to emerge with a prominent weakness in executive functions, with a corollary increase in health risk behaviours (Bousman et al., 2010). In general, to the extent that the clusters emerge as viable and valid, we anticipated significant between-group differences on the aforementioned risk factors and outcomes.

Method

Participants

Three hundred and fifteen individuals were recruited from four different SRO hotels, located in the Downtown Eastside of Vancouver British Columbia, as part of a 5-year longitudinal study. Inclusion criteria were living in an SRO hotel and being fluent in English. A total of 288 individuals completed baseline neurocognitive assessments, with 39 participants excluded because of missing or invalid data on more than one neuropsychological measure, yielding a final sample size of 249. A description of the sample is provided in Table 1. Ethics approval for the original study has been obtained from the Clinical Research Ethics Board of the University of British Columbia and the Simon Fraser University Office of Research Ethics. Approval for the current study has also been obtained from the Simon Fraser University Office of Research Ethics. All participants provided written informed consent.

Table 1. Sample Characteristics

Characteristic	%	Mean (SD)	Median	Range
Age (years)		43.5 (9.3)	44.0	23-68
Education (years)		10.4 (2.3)	10.0	3-16
Premorbid IQ (WTAR)		97.5 (8.9)	97.0	77-122
Symptoms of psychosis (PANSS)				
Positive		15.4 (5.7)	14.0	7-36
Negative		16.3 (6.2)	16.0	7-39
General		35.6 (8.5)	35.0	19-59
Total		67.3 (17.3)	65.0	33-129
Depressive symptoms (BDI)		11.7 (10.5)	9.0	0-46
Social functioning (SOFAS)		39.6 (10.5)	38.0	20-69
Role functioning (RFS)		12.0 (3.3)	12.0	5-24

Characteristic	%	Mean (SD)	Median	Range
Ethnicity ^a				
White	60.2			
Aboriginal	28.7			
Black	2.5			
West Asian	2.5			
Latin American	0.8			
Other/unknown	5.3			
Psychiatric diagnosis ^b				
Schizophrenia spectrum	12.7			
Other psychoses	20.4			
Major Depression	15.7			
Bipolar Disorder I or NOS	5.2			
Bipolar Disorder II	1.2			
Substance induced disorders	26.5			
Active psychosis at testing	46.7			
Substance Dependence Disorder ^b				
Alcohol	16.5			
Cannabis	33.7			
Cocaine	70.7			
Methamphetamine	23.3			
Heroin	35.7			
Viral infection				
HIV ^c	16.7			
Hepatitis C ^c	70.3			
Hepatitis B ^d	41.0			
Herpes simplex ^e	92.0			
Cytomegalovirus ^c	69.0			
Traumatic brain injury				
any reported head injury ^f	61.0			
with loss of consciousness ^e	31.3			
with memory loss/confusion ^e	19.3			

Note. WTAR = Wechsler Test of Adult Reading; PANSS = Positive and Negative Syndrome Scale; BDI = Beck Depression Inventory; SOFAS = Social and Occupational Functioning Assessment Scale; RFS = Role Functioning Scale; NOS = Not otherwise specified.

^a*n* = 244. ^b*n* = 245. ^c*n* = 239. ^d*n* = 229. ^e*n* = 238. ^f*n* = 241

Materials and Procedures

Neurocognitive Assessment

Neuropsychological tests of memory, attention, and executive abilities were administered to participants by trained research assistants. Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler, 2001). Verbal memory was assessed using the Hopkins Verbal Learning Test Revised (HVLTR; Brandt &

Benedict, 2001) immediate recall score. Sustained attention was measured using the signal detection (A prime) score from the Rapid Visual Information Processing (RVIP) subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996). Several different measures were used to index various aspects of executive function. First, the Color-Word subtest of the Stroop Color-Word Test was selected to measure response inhibition. Mental flexibility was evaluated by the total adjusted errors score from the Intra-Dimensional Extra-Dimensional (IDED) subtest of the CANTAB (Fray, Robbins, & Sahakian, 1996). Third, the Iowa Gambling Task (IGT; Bechara, Damasio, Damasio, & Anderson, 1994) total net score was employed to assess decision-making skills and response to reward. Further details regarding collection of background data and neurocognitive measures can be found in Appendix A.

Clinical Assessment

In a separate session with the participants, trained research assistants and psychiatrists conducted a clinical assessment. A number of clinical variables were selected to compare the derived cluster groups on, including putative risk factors of cognitive dysfunction and core clinical and functional outcomes.

Risk Factors

To retrospectively quantify substance consumption (alcohol, cocaine, methamphetamine, heroin) in the previous 30 days, the Time Line Follow Back method (TLFB; Sobell, Sobell, Klajner, Pavan, & Basian, 1986) was employed. The TLFB interview was conducted on a monthly basis and an average was computed to index the mean days per month of substance consumption around the time of cognitive testing (one month preceding, current month, one month proceeding¹). Diagnoses of psychiatric disorders and substance use disorders were made according to the

¹ Due to unavailability for follow-up, 36.1% of participants had TLFB data available for only two months, while 4.8% had TLFB data for one month. 6.8% of participants were missing TLFB for all three months surrounding the date of cognitive testing.

Diagnostic and Statistical Manual of Mental Disorders (4th ed., text revision; DSM-IV-TR; American Psychiatric Association, 2000) through consensus with the Best Estimate Clinical Evaluation and Diagnosis (BECED; Endicott, 1988) using all available data, including a diagnostic interview with the Mini-international neuropsychiatric interview (Sheehan et al., 1998) and a mental status examination by a psychiatrist (see Table 1 for incidences of the primary diagnoses). To index viral infection status, participants provided blood samples for ascertainment of anti-body based viral serology for the following five viruses: HIV, HCV, hepatitis B, herpes simplex, and cytomegalovirus. Of note, seropositivity for HIV indicates current infection, whereas seropositivity for the other viruses represents an index of exposure and is indicative of either a current or past infection. Traumatic brain injury was assessed using a self-report medical questionnaire that indexes history of a head injury and whether it was accompanied by loss of consciousness and/or associated with memory loss and confusion.

Clinical and Functional Outcomes

Symptom severity of psychosis was measured using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987). For the current study, we examined Positive, Negative, and General Subscale Scores, with higher values indicative of more severe symptoms. A short version of the PANSS, administered on a monthly basis, was used to capture psychosis status at the month of cognitive testing. The Beck Depression Inventory 2nd Edition (BDI-II; Beck, Steer, & Brown, 1996) total score was used to measure depressive symptomatology. The Maudsley Addiction Profile (MAP; Marsden et al., 1998) was used to index health risk behaviours. Participants were asked to report the number of days that they engaged in injection drug use and the number of times that they shared a crack pipe within the previous 30 days. For this same time interval, the number of unprotected sexual partners and the number of times participants engaged in sexual intercourse without using a condom were recorded. These latter two indexes were multiplied to mitigate the potential effect of individuals being involved in monogamous relationships in which a greater number of unprotected sexual encounters with the same partner may be perceived as low risk. To assess everyday functioning, the Social and Occupational Functioning Assessment Scale (Goldman, Skodol, & Lave, 1992) and the Role Functioning Scale were administered. Total scores from each measure were used, with higher scores indicative

of better functioning. Additional details pertaining to the clinical measures used in this study are reported in Appendix B.

Statistical Analyses

Prior to running the cluster analysis, a log transformation was applied to the IDED total adjusted errors score to correct a severe positive skew. These scores were then multiplied by -1 so that negative scores would reflect poorer performance, in keeping with the interpretation of other cognitive scores. To control for the effects of age and education, these variables were regressed on scores for HVL, RVIP, Stroop, IDED, and IGT using five separate regression analyses (see Manly et al., 2011 for a similar approach). The standardized residuals (z-scores) generated for each cognitive variable were used as the dependent variables in the cluster analyses and the discriminant function analysis.

Following the guidelines set forth by Lange, Iverson, Senior, and Chelune (2002) a two-step cluster analysis was conducted using Statistical Package for the Social Sciences (SPSS) 19.0. This step-wise process has been demonstrated to promote the best cluster recovery (Milligan, 1980). First, two different hierarchical cluster analyses (Ward's method, Average Linkage method) were employed as a means to determine the number of clusters present in the sample. Hierarchical algorithms begin with each case as a separate cluster (for a total of N clusters) and successively merge clusters, based on similarity across the specified set of variables, until a single cluster remains. The final number of clusters was determined by visually inspecting the dendrogram for natural breaks in the merging of clusters - a widely accepted method of determining the number of clusters in a data set (e.g. Clatworthy, Buick, Hankins, Weinamn, & Horne, 2005; Lange et al., 2002). A large break in the dendrogram signifies that further merging of the clusters may no longer be meaningful. Hierarchical algorithms are often used when the number of clusters within a dataset is unknown. The squared Euclidean distance coefficient was selected as the proximity measure because it addressed both profile shape and elevation when assigning cluster membership (Everett, Landau, Leese, & Stahl 2011). This measure was most relevant to the current study because differences in the magnitude of cognitive functioning between groups as well as the pattern of

functioning within groups were of interest. As a second step, a k-means algorithm using random seed points was employed to facilitate optimal assignment of cluster membership (Lange et al., 2002), specifying 3 clusters as determined by the hierarchical dendrograms. The k-means algorithm begins by selecting a random starting point (centroid) for each cluster and assigns cases based on their proximity to the centroid. A number of iterations are performed and cases are reassigned until the cases within each cluster are optimally similar and the distance between each cluster centroid is maximized.

Supplementary to the cluster analysis, a direct discriminant function analysis (DFA) was conducted to determine whether there were any relationships between the six neurocognitive variables that were accounting for separation between the three cluster groups, and to evaluate the accuracy of these relationships in classifying the cases. Additionally, this technique enables identification of the cognitive variables that are most important for distinguishing between cluster groups. This supplementary approach has been used in similar studies using neuropsychological data (e.g. Delano-Wood et al., 2009; Hermens et al., 2011).

In accordance with best practices, the internal validity of the final cluster solution was examined by constructing a multi-profile multi-method correlation matrix using profile means generated from the hierarchical and k-means algorithms. This approach ensures that the clusters derived from one algorithm are consistent with those derived from alternative algorithms, rather than being a mere artefact of the statistical procedure. Significant, positive correlations among the corresponding profiles from different algorithms are indicative of good internal cluster validity (Lange et al., 2002). Likewise, non-significant or negative correlations between non-corresponding profiles across algorithms suggest dissimilarity and also support the internal validity.

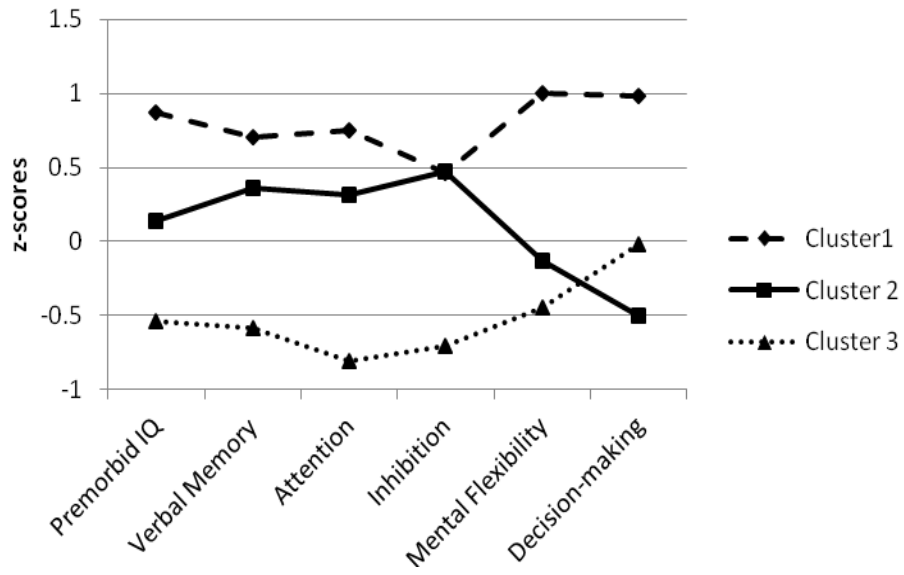
The external validity of the derived clusters was evaluated by comparing groups on demographics and external variables to determine if they differed in ways that were consistent with the broader neuropsychological literature that demonstrates associations between cognition and various risk factors and outcomes. Analysis of variance (ANOVA) was used to compare clusters on continuous variables, which included age, education, monthly substance use, total viral exposure, clinical symptomatology, health

risk behaviours, and everyday functioning. Non-parametric procedures were used when the assumption of normality was violated. Chi-square analyses were employed for categorical data, which included gender, DSM-IV-TR diagnoses, psychosis status at testing, HIV and HCV infection status, and history of a traumatic brain injury. Post-hoc tests were used to examine sources of specific differences. The alpha level was set to .05 and a Bonferroni correction was applied when multiple comparisons were made within a given domain (e.g. diagnoses, symptoms of psychosis) and for post-hoc comparisons. Trends are reported for significant group differences that did not withstand a Bonferroni correction. The error-wise alpha levels for each domain of comparisons can be found in Table C1 of Appendix C. Effect sizes (ESs) were calculated for each significant pairwise comparison using d (mean difference/mean standard deviation) for ANOVAS (corresponding to ESs of small = .2, medium = .5, large = .8; Cohen, 1992), r for non-parametric analyses (corresponding to ESs of small = .10, medium = .3, large = .5; Cohen, 1992), and the odds ratio for chi-square analyses. Additional details pertaining to the statistical procedures can be found in Appendix D.

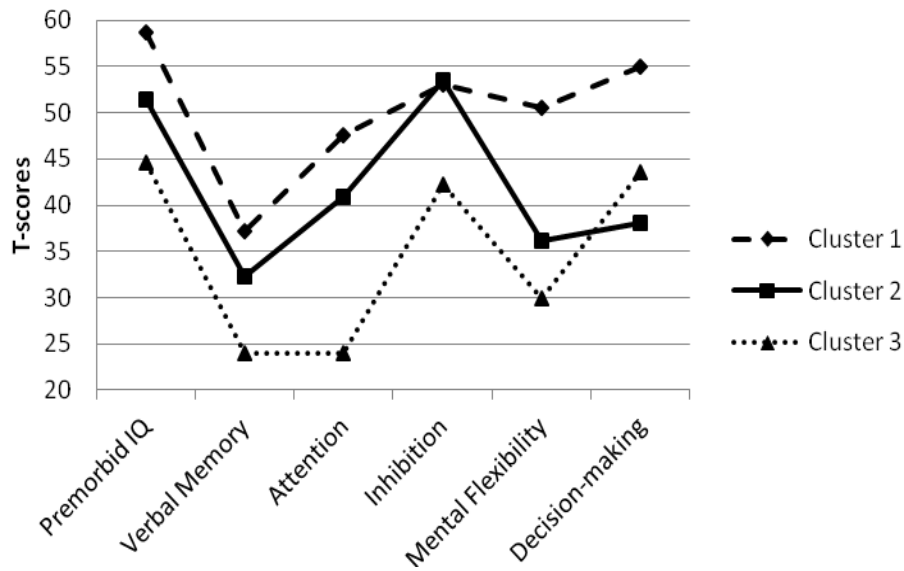
Results

Cluster Analysis

No differences were found between included and excluded cases (due to invalid or missing cognitive data) on age or education, $p_s > .05$. The two-step cluster analysis revealed a three cluster solution to be optimal (Cluster 1: $n = 59$ (23.7%); Cluster 2: $n = 103$ (41.4%); Cluster 3: $n = 87$ (34.9%)). The neurocognitive profile for each cluster is shown in Figure 1a, with the group mean plotted for each variable. For illustrative purposes, Figure 1b provides corresponding demographically corrected T-score profiles based upon the established normative test references. Profiles are described in terms of strengths and weaknesses when a given mean differs from the overall mean score (across the six cognitive variables) of its respective profile, by at least .5 absolute standard deviations (see Dawes et al., 2008). Cluster 1, the smallest group, is characterized by a higher level of neurocognitive functioning across domains relative to the other clusters (see Figure 1a). Normatively, this cluster exhibits strong estimated premorbid IQ and shows most cognitive abilities falling within normal limits, with a prominent impairment (i.e., greater than 1SD below the mean) in verbal memory (see Figure 1b). Cluster 2, the largest group, is characterized by functioning that generally bisected the other two cluster groups, but with a relative weakness in decision-making skills. The corresponding normatively-based profile suggests verbal memory is the most impaired domain of functioning, falling well below average. Nonetheless, attention, mental flexibility, and decision-making abilities are also impaired, with average range premorbid IQ estimate and inhibitory control. Finally, Cluster 3 is marked by the lowest functioning overall, compared to the other clusters, with a relative strength in decision-making skills. The normative profile further suggests that verbal memory, attention, and mental flexibility performances are within the impaired range. Nonetheless, the premorbid IQ estimate falls within normal limits.



a. using uncorrected z-scores.



b. using demographically corrected T-scores

Figure 1. Profiles of means for neurocognitive measures by cluster group

Discriminant Function Analysis

Two discriminant function (DF) variates were generated and both contributed significantly to separation of the three cluster groups. The first DF accounted for 81.1% of the between-group variance, Wilk's lambda = .166, $p < .001$. The second DF accounted for the remaining 18.9% of the variance, Wilk's lambda = .614, $p < .001$. The most substantial contributors to the first DF variate (in descending order) were tests of sustained attention, premorbid IQ, verbal memory, and mental flexibility. Tests of decision-making and inhibition made the greatest contribution to the second DF. The overall DFA model correctly classified 98.7% of cases, with 100% correct classifications for Clusters 1 and 3, and 97% correct classifications for Cluster 2. To eliminate bias in the classification of cases, the leave-one-out (jackknifed) classification procedure was employed as a cross-validation method. The overall correct classification of cases with this approach was marginally lower than the original model at 96.6%, with 96.6% correctly classified for Cluster 1, 94% correct for Cluster 2, and 100% correct for Cluster 3.

Cluster Validation

Internal Validity

The multi-profile multi-method correlation matrix is displayed in Table 2. Overall, the profiles derived from the three different algorithms employed positively correlate with their respective profiles generated by each algorithm, while demonstrating non-significant or negative correlations with non-corresponding profiles, suggesting adequate internal validity².

² Only one bivariate relationship did not correspond as expected. Profile 1 of the K-means algorithm correlated more strongly with profile 3 of the Ward's algorithm, as oppose to Ward's profile 1 (see Table 2).

Table 2. Multi-profile Multi-method Correlation Matrix

Profile	Ward's Method			Average Linkage Method			K-means Method		
	wH1	wH2	wH3	aH1	aH2	aH3	K1	K2	K3
wH1	1.00								
wH2	-.49	1.00							
wH3	.20	-.83	1.00						
aH1	.75	-.75	.29	1.00					
aH2	-.20	.89	-.89	-.46	1.00				
aH3	-.26	-.55	.75	-.04	-.84	1.00			
K1	.49	-1.00	.83	.75	-.89	.55	1.00		
K2	-.26	.94	-.77	-.67	.94	-.70	-.94	1.00	
K3	-.03	-.77	.94	.20	-.94	.90	.77	-.83	1.00

Note. Correlations were computed using Spearman's Rho; wH = Ward's hierarchical analysis; aH= Average Linkage hierarchical analysis; K= K-means analysis; Boldface denotes the largest positive correlation between a given profile and one of the three profiles derived from an alternative method

External validity

Table 3 summarizes the significant differences observed between groups, pairwise comparisons, and the corresponding effect sizes. In brief, Cluster 1 was associated with significantly higher years of education, a greater proportion of heroin dependent individuals, and less severe negative symptoms relative to Cluster 3, with an overall lower rate of HIV infection. On the other hand, Cluster 2 was comprised of individuals who reported significantly more days per month of heroin use and was marked by a higher proportion of individuals with heroin dependence, when compared to Cluster 3. Additionally, there were trends towards a greater proportion of females in Cluster 2, as well as more injection drug use, less alcohol use, and more severe negative symptoms when compared to Cluster 1. Cluster 3 was characterized by lower education, more severe negative symptoms, and exposure to a greater number of viruses relative to Cluster 1, with an overall lower rate of heroin dependence and less heroin use. Effect sizes ranged from small to medium-large. No significant differences were found between clusters on age, diagnoses of psychiatric illnesses or substance dependence disorders (other than heroin dependence), days per month of drug use (other than heroin use), HCV infection, depressive symptoms, risky sexual behaviours, or everyday functioning ($ps > .05$). A summary of the results by cluster group is provided in Table 4.

Table 3. Significant Between-group Differences for External Validation Variables

Variable	Cluster			Test statistic	Comparisons	Effect size
	1 (n=59, 23.7%)	2 (n=103, 41.4%)	3 (n=87, 34.9%)			
Education (M, SD)	11.10 (2.23)	10.33 (2.39)	10.00 (2.04)	F = 4.35*	1>3	d = 0.52
Gender (% male)	86.44	69.90	81.61	$\chi^2 = 7.02^*$	2>1†	OR = 2.74
Mean alcohol days (Mdn, IQR)	0.83 (4.42)	0.33 (1.00)	0.67 (5.58)	H = 7.21††	3>2†; 1>2	r = 0.18; 0.17
Mean heroin days (Mdn, IQR)	0.00 (12.00)	0.33 (9.33)	0.00 (1.13)	H = 9.29**	1>3†; 2>3	r = 0.20; 0.22
Heroin dependence (%)	40.68	44.66	21.84	$\chi^2 = 11.50^{***}$	1>3; 2>3	OR = 2.45; 2.91
Days injected (Mdn, IQR)	2.00 (30.00)	4.00 (21.00)	0.00 (6.00)	H = 7.89††	2>3	r = 0.21
HIV infection (% +)	3.39	16.50	24.14	$\chi^2 = 11.10^{***}$	2>1; 3>1	OR = 5.60; 9.01
Total virus exposure (M, SD)	2.52 (1.08)	2.85 (1.16)	3.21 (1.22)	F = 5.76***	3>1	d = 0.60
PANSS (M, SD) Negative symptoms	13.88 (4.25)	16.20 (6.63)	17.92 (6.11)	F _{BF} = 7.83***	3>1; 2 >1†	d = 0.78; 0.43

Note. OR = odds ratio; IQR = Interquartile range; PANSS = Positive and Negative Syndrome Scale; Mean alcohol days = group median of the mean number of days per month of alcohol use; Mean heroin days = group median of the mean number of days per month of heroin use; Days injected = group median of the number of days of injection drug use in the past 30 days.

†Not significant following a Bonferroni correction.

*p<.05. **p<.01. ***p<.005.

Table 4. Summary of Results

	Cluster 1	Cluster 2	Cluster 3
Neurocognition	Highest functioning group within the sample. Normatively, strong premorbid IQ, and average range attention and executive functions, with impaired memory.	Intermediate functioning group within the sample, with a relative weakness in decision-making skills. Normatively, average range premorbid IQ, attention, and inhibition, with impairments in memory, mental flexibility, and decision-making skills.	Lowest functioning group within the sample, with a relative strength in decision-making skills. Normatively, average range premorbid IQ, inhibition, and decision-making skills, with impairments in attention, memory, and mental flexibility.
External variables	More years of education, lower rate of HIV infection, lower total virus exposure, and less severe negative symptoms.	More heroin use, with trends towards more females, more injection drug use, less alcohol use, and more severe negative symptoms.	Less years of education, less heroin use, lower rate of heroin dependence, greater total virus exposure, and more severe negative symptoms.

Discussion

The current study identified three distinct neurocognitive profiles, within a large sample of SRO residents. The characteristics of this sample were consistent with what has been reported in other marginally housed (Robertson et al., 2004) and homeless populations (Fazel, Khosla, Doll, & Geddes, 2008), with similar demographic features and comparable rates of substance use, HIV infection, psychotic illness, and major depression. The findings generally supported our initial expectations regarding the profiles and their associated features. Indeed, differences in the magnitude of cognitive functioning emerged, with Clusters 1 and 3 characterized by overall higher and lower functioning respectively. As anticipated, Cluster 3 evidenced increased clinical symptomatology in the form of more severe negative symptoms, but not depressive symptoms, when compared to the higher functioning Cluster 1. Likewise, as expected, a profile emerged with a relative weakness in executive functions, whereby Cluster 2 demonstrated the poorest decision-making ability with a trend toward increased health risk behaviour in the form of more days of injection drug use in the past 30 days.

To summarize, Cluster 1 (n = 59) emerged as the smallest group with overall higher cognitive functioning relative to the other derived clusters. Compared to standard norms, this group exhibited functioning within normal limits except for impairment in verbal memory. This profile is in keeping with Cluster 1's higher years of education, as well as the lower incidence of HIV infection and less severe negative symptoms. These associated features, in conjunction with Cluster 1's strong premorbid IQ estimate might be considered an indicator of good cognitive reserve. Indeed, better premorbid intellectual functioning has been linked to a lower likelihood of engaging in health risk behaviour that leads to HIV infection in opiate users (Mitchell, Severtson, & Latimer, 2007).

In contrast, Cluster 2 (n = 103) emerged as the largest group and is best described as functioning intermediate to the other clusters in the sample, with a relative weakness in decision-making skills. Compared to standard norms, Cluster 2 is

functioning below normal limits, but nonetheless exhibits average range premorbid IQ estimate and inhibition. Such a discrepancy between premorbid abilities and current functioning might suggest that the existing impairments are a result of substantial brain insult from exposure to adverse environmental events. Cluster 2, with its prominent decision-making deficit, was accompanied by elevated rates of heroin use and dependence, with a trend towards more injection drug use. This pattern might suggest that individuals are driven to engage in health risk behaviours on the basis of immediate reward as opposed to long-term adverse consequences (see Bechara, 2003 for review), and may be indicative of dysregulated frontal brain circuitry (Ersche et al., 2005). Furthermore, individuals in Cluster 2 demonstrated an elevated rate of HIV infection, a feature that has been previously linked to health risk behaviour in the marginally housed (Aidala et al., 2005; Robertson et al., 2004).

Finally, Cluster 3 ($n = 87$) emerged with overall lower cognitive functioning when compared to the other clusters, with a relative strength in decision-making skills. Normatively, this group is highly impaired, but nonetheless exhibits premorbid IQ, inhibition, and decision-making abilities in the average range, albeit mildly weaker relative to the other groups. This pattern of a slightly attenuated premorbid IQ estimate with several domains of impaired cognition could be indicative of relatively lower cognitive reserve in Cluster 3. Correspondingly, Cluster 3 was further characterized by lower years of education and greater total virus exposure, relative to the higher functioning Cluster 1, in addition to overall less heroin use and dependence, and more severe negative symptoms. These findings are consistent with evidence that suggests poorer cognitive performance in individuals with psychosis who exhibit worse negative symptoms (Dominguez et al., 2009; Lindsberg et al., 2009), and in persons with comorbid viral infections (Cherner et al., 2005; Letendre et al., 2005; Martin-Thoymeyer & Paul, 2009; Richardson et al., 2005). Overall, the clusters derived from this analysis appear robust and viable. Rigorous validation methods revealed that consistent neurocognitive profiles could be rendered using three different clustering algorithms. This suggests that these profiles are likely not an artefact of the statistical procedure itself, but rather these profiles represent meaningful subgroups, within a heterogeneous sample, that can be reliably differentiated on external factors. Moreover, the discriminant function analysis suggested that all six of the neurocognitive variables were

important for distinguishing between groups, and might be conceptualized as representing two underlying cognitive dimensions.

Although the resultant profiles and associated features were mostly in keeping with our original expectations and were supported by the existing literature, we did not observe any differences between the derived cluster groups on depressive symptoms. Thus, it is likely that other external variables, such as negative symptoms, may be more important for distinguishing between groups. Interestingly, we also did not find any meaningful differences in everyday functioning across the clusters even though cognition has demonstrated to be a robust predictor of functional outcomes in a variety of populations (Fett et al., 2011; Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Kalechstein, Newton, & van Gorp, 2003; Morgan & Heaton, 2009). However, it appears that this sample as a whole is functioning at a lower level, leading to a truncated range of scores and reduced variability on the measures used (see Table 1). It is possible that a more nuanced measure of everyday functioning that is sensitive to gradations in activities of daily living would better capture differences across the derived neurocognitive profiles. Indeed, complex everyday tasks, such as financial and medication management, might be better assessed with novel measures that demonstrate good ecological validity (Scott et al., 2011). Alternatively, it may be that cognition is not associated with everyday functioning in this sample of SRO residents because the demands of their environment may be both quantitatively and qualitatively different from what is observed in stably housed populations. Further, the individual differences in cognitive profiles may be largely irrelevant because heterogeneous patterns of substance abuse predominantly drive the variation in everyday functioning and render cognition non-contributory. The differential impact of substance use on cognition and everyday functioning warrants further exploration.

To our knowledge, this is the first study to identify and describe profiles of neurocognitive functioning in a marginalized population. This approach could be a useful tool in determining which subgroups of individuals are at risk for poorest long-term outcomes and elucidate modifiable targets for intervention programs. Certainly, individuals with the lowest premorbid functioning (e.g., low cognitive reserve) showed widespread neurocognitive impairments and are apt to require additional resources to cope with the burden of multiple comorbidities compared to higher functioning individuals

with better cognitive reserve. More specifically, the lowest functioning group might require greater outreach and structured treatment especially since the profile was associated with greater negative symptoms that may further exacerbate their engagement in a complex health care system. Likewise, individuals with selective impairments in decision-making ability may require more targeted interventions that address the specific consequences of their cognitive weaknesses and the putative risk factors that contribute to those impairments. Indeed, Cluster 2's impaired decision-making ability was accompanied by more injection drug use and higher rates of HIV infection. Addressing the decision making impairments of these individuals may be crucial to successful interventions that promote safe health behaviour and prevent infection. Overall, these findings are especially relevant for clinicians in that they highlight the need for interventions that address the unique cognitive profiles of the groups in their interface with complex clinical and behavioral complications.

Importantly, this study shows that cognition can provide the basis for identifying meaningful subgroups within a heterogeneous sample of marginalized persons. To date, only a handful of studies have examined cognitive functioning in homeless populations (e.g. Burra, Stergiopoulos, & Rourke, 2009), but no studies have employed an exclusive sample of marginally housed persons. What is more, many of these studies were limited by the use of screening measures of cognition, such as the Mini-Mental State Examination (e.g. Adams, Pantelis, Duke, & Barnes, 1996; Fichter & Quadflieg, 2001), as opposed to characterizing functioning across a broad array of domains. Thus, this study provides an important foundation for which future research can build upon. Indeed, the results aptly convey how diverse this group is, yet at the same time, how cognitively impaired these individuals are. As illustrated in Figure 1b, the three cluster groups presented with profiles that might be characterized as memory impaired, with performance that falls one standard deviation below the normative mean. Additionally, Clusters 2 and 3 exhibited profiles that suggest prominent deficits in other domains of functioning, and in some cases, are of considerable magnitude at two standard deviations or more below the mean.

Nevertheless, limitations of this study should be considered. First, as this was an exploratory study, it is possible that some of the differences observed between clusters were spurious, despite rigorous control of error inflation. Thus, this study warrants

replication. Second, although the test battery employed was comprised of valid standardized measures that represent a broad array of cognitive domains, it is possible that additional neuropsychological measures might better characterize groups. Specifically, more traditional measures of executive functions, as opposed to computerized tasks like the CANTAB and IGT, could further define profiles and elucidate between-group differences on risk factors and outcomes. Conversely, the multivariate profiles may not be suitable for examining all associations between cognition and external factors, and scores on unitary cognitive domains may inevitably be better predictors of certain clinical and functional outcomes. It is also noteworthy to mention that the neurocognitive testing may have been vulnerable to the effects of acute intoxication, given that many of the participants reported daily use of substances. The ingestion of substances, in some cases, may have been temporally proximal to the testing session and could have led to transient impairment in cognitive functioning, resulting in an underestimation of true cognitive abilities. Subjective validity ratings of each cognitive measure, however, were used to exclude participants that appeared intoxicated or were unable to exert reasonable effort and adequately engage in testing. Nonetheless, since daily substance use is a prominent feature of this sample, the residual positive (e.g., heightened alertness) and negative effects of substance use are apt to represent the baseline state of these individuals. Future studies should aim to evaluate the extent of cognitive impairment in this SRO sample by comparing it to a sample of healthy controls. Additionally, linking the neurocognitive profiles to underlying brain pathology using neuroimaging techniques could provide further insight into the nature of the subgroups within this sample.

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Appendices

Appendix A.

Background Information

Demographic data, including age, gender, ethnicity, and education, were obtained at the time of cognitive testing by trained research assistants. The total years of education was indexed using the guidelines provided by Heaton, Miller, Taylor, and Grant (2004). English fluency was measured using a 12-item acculturation questionnaire assessing the degree to which English is primarily used for thinking, reading, writing, and speaking. Scores can range from 12 (very fluent in English) to 60 (not at all fluent in English). A score of 24 indicates that, on average an individual is *much fluent in English*, and was used as a cut-off in determining whether participants were deemed to be fluent in English. Only one case had a fluency score greater than 24, but was nonetheless deemed to be fluent in English, and was retained for the analyses.

Cognitive Measures

At the time of testing, the examiner subjectively rated the validity of each completed test on a scale ranging from 0 (clearly invalid) to 5 (completely valid). Participants were excluded if: two or more cognitive tests were assigned a rating below 4 (most likely valid), two or more tests were not completed, or any combination of the above affecting at least two cognitive tests. This exclusion rule was established so that participants with invalid and/or missing data on at least 33% of the cognitive tests would not be assigned cluster membership.

Premorbid IQ

The WTAR (Wechsler, 2001) was selected as an estimate of intelligence prior to the onset of psychiatric illness and consists of a list of 50 irregularly spelled words (e.g. porpoise, gnat) which an examinee is asked to read aloud in a continuous fashion. The normative tables allow for an estimation of full scale IQ using the WTAR standard score, age, and education. The WTAR demonstrates excellent test-retest reliability with values exceeding .90 (Wechsler, 2001). Construct validity is also strong, as the WTAR correlates well with verbal and full scale IQ scores on the Wechsler Adult Intelligence Scale 3rd edition ($r = .75$ and $.73$ respectively). The WTAR is advantageous over other indices of premorbid IQ as it enables an estimate of full scale IQ (based on age and education) in the absence of complete WTAR data. This demographic predicted estimate was used for cases with incomplete WTAR data and for individuals with an English language fluency score greater than 24.

Verbal Memory

The HVLT-R (Brandt & Benedict, 2001) was used as a measure of verbal memory. Two alternate forms were administered (Versions 1 and 2) and were counterbalanced across participants. A list of 12 words, from three different semantic categories, was read aloud to participants for three consecutive trials. At the end of each trial, participants were immediately asked to recall as many words as they could. The number of words recalled was summed across trials, yielding a total score for immediate verbal memory that can range from 0 to 36, and was used for the current study. Test-retest reliability of the immediate recall scores has been deemed to be good ($r = .74$; Brandt & Benedict, 2001). The HVLT-R appears to be a valid test of verbal memory as it correlates with similar standardized neuropsychological measures, such as the California Verbal Learning Test and the Logical Memory component of the Wechsler Memory Scale ($r = .36$ and $.65-.77$, respectively).

Attention

The RVIP subtest of the CANTAB (Fray, Robbins, & Sahakian, 1996) was used to measure sustained attention. On a computer screen, participants viewed a series of digits, in a fixed position, presented one at a time in a pseudo-random fashion. Participants were required to detect a series of target sequences (e.g. 3-5-7, 2-4-6, 4-6-8) and to respond using a press pad. This task ran for approximately seven minutes. A coefficient of signal detection (referred to as A prime) was computed for use in this study. Test-retest reliability for the RVIP test is deemed to be good, with coefficients ranging from .76 to .80 (Fray, Robbins, & Sahakian, 1996; Lowe & Rabbitt, 1998).

Executive Functions

The Stroop Color-Word subtest of the Stroop Color-Word Test was selected to measure response inhibition. Participants were presented with a page of words that denoted colours (e.g. blue, red, green) but were printed in alternate colours of ink. Participants were instructed to verbalize aloud the colour of ink each word was printed in, while ignoring the word. The total number of correct responses provided in a 45 second time period was used for this study. The Stroop Color-Word test demonstrates adequate test-retest reliability values (.75) and correlates moderately with other measures of inhibition (Strauss, Sherman, & Spreen, 2006).

The IDED subtest of the CANTAB (Fray, Robbins, & Sahakian, 1996) was used to measure attentional set-shifting (mental flexibility). On a computer screen, participants were presented with two simple stimuli (shapes) and had to identify which one was correct by touching it on the screen. Feedback (correct versus incorrect) was provided to help the participant determine what the appropriate response (rule) was. The rule changed after six consecutive correct responses, but the participant was not made aware of when the change occurred, using only the feedback as a guide. At later stages, an extra dimension was added to the stimuli (lines) and the rule shifted between the two dimensions. There were a total of nine stages and each stage could only be successfully completed if a participant achieved six consecutive correct responses within 50 trials. The total number of errors (adjusted for stages completed) was calculated for the current study. The IDED task demonstrates adequate test-retest reliability of .70 (Lowe & Rabbitt, 1998).

The IGT (Bechara, Damasio, Damasio, & Anderson, 1994) was employed to assess decision-making skills and response to reward. On a computer monitor, participants were presented with four decks of cards (labelled A, B, C, and D). After each card selection, participants were provided with immediate feedback as to whether they won or lost a specific amount of money. A running total of gains and losses was displayed at the top of the screen using coloured bars, with the difference between these bars representing net earnings (may be positive or negative). Some card selections were associated with both reward (monetary gain) and punishment (monetary loss). Two of the decks were associated with both large monetary reward and large overall net loss, yet punishment occurred less often. The other two decks were associated with smaller monetary gains and the least amount of loss, but were associated with a higher frequency of punishment. However, the latter two decks are considered more advantageous as they result in an overall net gain. A total of 100 card selections were made to complete the task. A net score was computed for the current study, by subtracting the total number of selections made from the two disadvantageous decks from the total number of advantageous selections made. Satisfactory construct validity of the IGT has been established through lesion and imaging studies in which IGT performance is shown to correlate with either damage or neural activity in the ventral medial and orbitofrontal regions; areas known to mediate decision-making behaviour (Buelow & Suhr, 2009).

Appendix B.

Clinical Measures

Substance Use

Data pertaining to substance use was acquired at monthly intervals using the TLFB method (Sobell, Sobell, Klajner, Pavan, & Basian, 1986). The TLFB is a retrospective interview procedure originally designed to quantify alcohol consumption within a specified calendar interval. This procedure has demonstrated strong test-retest reliability ($r = .70-.98$) and converges well with other measures of alcohol use (Cervantes, Miller, & Tonigan, 1994). Separate TLFB interviews were conducted for use of alcohol and illicit drugs. Three month averages surrounding the time of cognitive testing were computed separately for use of alcohol, cocaine, methamphetamine, and heroin. A two month average or a single month value was used when data was missing.

Psychiatric Symptoms

Symptom severity of psychosis was measured at baseline using the PANSS (Kay, Fiszbein, & Opler, 1987); a 30-item questionnaire, with each item rating symptomatology from 1 (absent) to 7 (extreme). There are seven items on each of the Positive and Negative Subscales. All remaining items make up the General Subscale, with total scores ranging from 30 to 210. The PANSS is used extensively with psychotic populations and demonstrates moderate to good test-retest reliability for both Negative and Positive Subscales, with correlations of .68 and .80 respectively. Adequate validity has been demonstrated through correlations with other measures of clinical symptoms and by correlating scores with observed changes in symptoms due to pharmacological interventions. A short version of the PANSS, consisting of four items from the Positive Subscale of the full PANSS and one item from the General Subscale, was administered monthly to assess psychosis status. A clinical decision was made by a research psychiatrist as to whether a participant was actively psychotic based on their short PANSS score. The psychosis status rated on the month of cognitive testing was used for analyses. If data for this time point were unavailable, we first looked to use data collected in the month preceding cognitive testing, and second to data collected in the month following cognitive testing. If no data were available for any of the three time points, then psychosis status was not included for that case.

Depressive symptoms were measured using the BDI-II (Beck, Steer, & Brown, 1996). The BDI-II was administered monthly, so data acquired on the same month as the cognitive testing were used for this study. If data for this time point were unavailable, we first looked to use data collected in the month preceding cognitive testing, and second to data collected in the month following cognitive testing. If no data were available for any of the three time points, then a BDI score was not included for that case. Test-retest reliability for the BDI-II is excellent ($r = .93$) and it correlates well with other measures of depression, such as the Beck Hopelessness Scale ($r = .68$) and the Hamilton Psychiatric Rating Scale for Depression ($r = .71$; Beck, Steer, & Brown, 1996).

Health Risk Behaviours

The MAP (Marsden et al., 1998) was used to examine health risk behaviours in the current study, and was specifically developed as a 60-item brief assessment tool for substance addicted populations with the aim to evaluate functioning across four different domains: substance use, health risk, physical and psychological health, and social functioning. For the current study only

health risk variables will be examined, indexing behaviour in the 30 days prior to interview. The MAP is conducted on a monthly basis, so scores on this measure were taken from the MAP conducted on the same month as the cognitive assessment. If data for this time point were unavailable, we first looked to use data collected in the month preceding cognitive testing, and second to data collected in the month following cognitive testing. If no data were available for any of the three time points, then MAP data was not included for that case. Test-retest reliability is good to excellent across the four domains, with correlations ranging from .77 to .95 (Marsden et al., 1998). Validity of the MAP is demonstrated through factor analysis which supports the presence of four independent dimensions.

Everyday Functioning

The Social and Occupational Functioning Assessment Scale (SOFAS) enables clinicians to rate participants' everyday functioning on a continuum ranging from 0 (inadequate information) to 100 (superior functioning in a wide range of activities) while taking into account impairments that are a direct consequence of a mental illness. The development of the SOFAS scale is described by Goldman, Skodol, and Lave (1992) and can be found in the DSM-IV-TR (American Psychiatric Association, 2000).

The Role Functioning Scale (RFS) consists of four subscales that measure working productivity, independent living/self care, immediate social network relationships, and extended social network relationships. Each subscale ranges from 1, indicating severely limited functioning in a given domain, to 7, indicating optimal performance in a given domain. Subscale scores are summed to produce a total RFS score, with possible values ranging from 4 to 28. The RFS has demonstrated strong test-retest reliability ($r = .85$ to $.92$) and good construct validity, as it correlates well with measures of global impairment and self-esteem (Goodman, Sewell, Cooley, & Leavitt, 1993). It also appears to discriminate well between individuals who are psychiatrically ill versus those who are well.

Appendix C.

Table C1.
Familywise Alpha Levels for Multiple Comparisons

Variables by domain	Familywise alpha level ($p < .05/n$)
Average monthly substance use days	.013
Alcohol	
Cocaine	
Methamphetamine	
Heroin	
Substance dependence disorders	.013
Alcohol	
Cocaine	
Methamphetamine	
Heroin	
Viral infection	.017
HIV	
Hepatitis C	
Total virus exposure	
Psychiatric illness	.010
Schizophrenia spectrum	
Other psychoses	
Major Depression	
Bipolar I or NOS	
Bipolar II	
Traumatic brain injury	.025
with loss of consciousness	
with memory loss/confusion	
Psychotic symptoms (PANSS)	.017
Positive	
Negative	
General	
Health risk behaviour (MAP)	.017
Days injected	
Times shared a crack pipe	
Unprotected sex*Unprotected partners	

Note. NOS = Not otherwise specified; PANSS = Positive and Negative Syndrome Scale; MAP = Maudsley Addiction Profile.

Appendix D.

Assumption Checking

Prior to running the cluster analysis, normality of each cognitive variable was checked using the Kolmogorov-Smirnov test and via visual inspection of the histogram. The assumption of homogeneity of variance-covariance matrices, as it pertains to the discriminant function analysis (DFA), was tested using Box's M. Although this test is highly sensitive, and DFA is typically robust to such violations in large samples, we nevertheless exercised appropriate caution by using separate covariance matrices for the purpose of classifying cases as a result of a significant Box's M test. Normality of the bivariate relationships for the correlation matrix was visually examined using a matrix of scatterplots. For the external validation of clusters, all continuous variables were examined for normal distributions by visual inspection of the histograms. Variables with non-normal distributions were subjected to Kruskal-Wallis nonparametric analyses. Cases with missing data on an external variable were excluded analysis-by-analysis.