An Investigation of Profiles of Polysubstance Use in Homeless & Precariously Housed Individuals

By

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Abstract

Despite the prevalence of polysubstance use among homeless and precariously housed persons, the cognitive and functional consequences of substance use patterns are poorly understood. This may be due in part to the limitations of existing work that attempts to isolate substances (e.g. methodologically or statistically) or lacks granularity (e.g. cross-sectional or lacking frequency of use). As such, this study aimed to improve upon past work by evaluating naturally occurring patterns of polysubstance use longitudinally. Using cluster analysis, this study revealed three validated substance use profiles: Frequent Heroin with Moderate Methamphetamine Use, Frequent Cannabis Use, and Infrequent to Moderate Polysubstance Use. Mixed general linear models indicated that the use profiles were not associated with differences in cognitive trajectory or capacity, however, persons engaged in frequent use showed poorer social and occupational functioning compared to a moderate use group. Implications are discussed.

Keywords: polysubstance use; neurocognition; everyday functioning; comorbidities; precarious housing; memory; processing speed; executive function; cluster analysis

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Table of Contents

List of Tables

List of Figures

Introduction

The cognitive and functional consequences of polysubstance use in homeless and marginally housed individuals are poorly understood. Homelessness is a known risk factor for substance use and vice versa (Bhalla, Stefanovics, & Rosenheck, 2017; Grinman et al., 2010). Statistics Canada reported a 21.6% lifetime prevalence and 4.4% one-year prevalence of substance use disorder for individuals aged 15 years and older (Statistics Canada, 2012). In contrast, among a sample of marginally housed and homeless individuals residing in Vancouver, British Columbia, 95.2% of all participants exhibit substance dependence (Vila-Rodrgiguez et al., 2013). Among individuals engaged in substance use, use of more than one type of substance is common (Connor, Gullo, White, & Kelly, 2014; John et al., 2018; Leri, Bruneau, & Stewart, 2002; Staines, Magura, Foote, Deluca, & Kosanke, 2008). Further, polysubstance use is often accompanied by more medical and psychiatric difficulties than single use disorders (Bhalla, Stefanovics, & Rosenheck, 2017; John et al., 2018; Tsai, Kasprow, & Rosenheck, 2010). The prevalence of polysubstance use, particularly of illicit substances (e.g. heroin, methamphetamine) is an important health concern in homeless and precariously housed persons given its prevalence in these groups. Evaluating the concomitant impact of polysubstance use is critical given the complex relationships that exist between use of various substances. Elucidation of profiles of substance use and associated demographics and comorbidities provides a potentially fruitful avenue for studying the complex cognitive and functional consequences associated with polysubstance use in a precariously housed sample. The present study occurs in two stages: Study 1 is an exploratory analysis, characterization, and validation of substance use profiles; Study 2 is an investigation of the cognitive and functional outcomes associated with use profiles.

Study 1

1.1. Introduction

Despite an extensive literature on the consequences of substance use, investigation into polysubstance use profiles is limited. Latent class analysis has been used to profile polysubstance use among a variety of populations (Connor, Gullo, White, & Kelly, 2014; Fernandez-Calderon et al., 2011; Harrell, Mancha, Petras, Trenz, & Latimer, 2012; Harrell et al., 2014; Kuramoto, Bohnert, & Latkin, 2011; Monga et al., 2007; Patra, Fischer, Maksimowska, & Rehm, 2009; Trenz et al., 2013). However, these approaches lack granularity as they are limited to dichotomous variables at a single time point (e.g. cocaine use in the last 6 months, Y/N). Given the complexity of polysubstance use and its associated cognitive and functional outcomes, evaluating the consequences of profiles of substance use is arguably a more parsimonious and clinically relevant approach to the study of substance use than investigating single substances. By improving sampling of substance use (monthly report of days of use) and following individuals longitudinally, the current research improves upon on past work by investigating cluster profiles of substance use type and frequency over a one-year period. We were further able to extensively validate our clusters with other measures of substance use behaviour and evaluate current use profiles in the context of participants' substance use history. This was done in a sample of homeless and precariously housed individuals in Vancouver's Downtown Eastside (DTES) to identify differences in demographics and relevant risk factors and outcomes across profiles.

Study 1 Aim 1 (Cluster Analysis): To employ cluster analysis to ascertain one-year polysubstance use profile patterns for heroin, methamphetamine, cannabis, cocaine, and alcohol. *Study 1 Aim 1a (External Validation):* To externally validate profiles of self-reported substance use based on other measures of substance use behaviour. *Study 1 Aim 1a (External Validation) Hypothesis:* Cluster groups were expected to differ in concordance with findings from Study 1 Aim 1 (i.e. rates of diagnoses and acute use should reflect self-reported frequency of use). *Study 1 Aim 1b (Risk Factors & Outcomes):* To evaluate whether substance use profiles are associated with demographics, psychiatric diagnoses, or neurological health factors that may act as risk factors or outcomes of polysubstance use. *Study 1 Aim 1b (Risk Factors & Outcomes) Hypotheses:* Given that Study 1 was exploratory, we did not have prior hypotheses regarding profile group differences.

1.2. Method

1.2.1. Participants

The data for this project was collected as part of a larger ongoing study. The HOTEL Study is a longitudinal investigation of health and social outcomes of residents in the DTES of Vancouver, British Columbia (Honer et al., 2017; Vila-Rodriguez et al., 2013). Participants were recruited from low-income, single-room occupancy housing, community court, and the local hospital in the DTES (N = 538). The current sample (N = 236) is 23.7% female, has an age range of 21 to 75 (M = 44.80, SD = 12.25), and has a mean of 10.37 years of education (SD = 2.13). Demographics, substance use, viral infection, mental health diagnoses, and neurological health factors are summarized in Table 1.

Table 1. Sample Characteristics

Characteristic		M (SD)	Median	Range	%
Demographics	Age (years)	44.80 (12.25)	46.64	20-75	
	Gender (% Female)*				23.7%
	Education (years)	10.37 (2.13)	10.00	3-16	
	Estimated Premorbid IQ (WTAR)	98.64 (8.86)	99.00	73-122	
	Ethnicity				
	White				55.1%
	Aboriginal				27.5%
	West Asian				3.0%
	Other				14.4%
Substance Use †	IV use during observation year				59.7%
	Baseline daily use of tobacco [n=230]				82.6%
Age of Onset	Alcohol [n=231]	13.53 (3.81)	14.00	4-30	
	Cannabis [n=230]	14.10 (4.09)	14.00	5-44	
	Cocaine [n=228]	22.41 (9.07)	19.00	9-54	
	Opioid [n=211]	24.19 (9.52)	21.00	9-61	
	Amphetamine [n=192]	24.68 (10.72)	21.00	6-59	
Current Dependence	Alcohol [n=199]				15.6%
	Cocaine [n=201]				28.4%
	Cannabis [n=202]				26.7%
	Heroin [n=201]				32.3%
	Methamphetamine [n=201]				31.3%
Lifetime Dependence	Alcohol				55.9%
	Cocaine				72.9%
	Cannabis				48.7%
	Heroin				56.8%
	Methamphetamine				42.4%
Viral Infection	HIV [n=217]				16.6%
	Hepatitis B [n=213]				34.3%
	Hepatitis C [n=213]				46.5%
Current	Major Depressive Episode***				16.8%

Characteristic		M (SD)	Median	Range	%
Diagnoses †	[n=197]				
	Generalized Anxiety Disorder [n=200]				8.0%
	Manic Episode [n=198]				7.6%
	PTSD [n=197]				10.2%
	Substance-Induced Psychosis [n=184]				9.2%
	Psychotic Disorder‡ [n=196]				35.7%
Neurological Health	TBI with LOC				32.2%
	Stroke [n=230]				3.9%

Note. N = 236 unless otherwise specified.

† Dependence and mental health diagnoses based on the Mini International Neuropsychiatric Interview closest at one-year follow-up (Within 275 days, M (SD) = 41.96 (47.75) days) and BECED at study entry. ‡Schizophrenia, schizoaffective, and psychotic disorder not otherwise specified. *One individual identified as transgender.

Cognitive assessments were conducted on a yearly basis. As such, we examined substance use over a one-year period (182 – 564 days, M = 336.8, SD 76.13) between January 2014 and January 2019. This allowed us to monitor changes from a baseline assessment (T1) and a one-year follow-up (T2) between which substance use was monitored monthly. While we might expect a larger effect size for cognitive decline over a longer observation, our sample size and subsequent power decreases with each year of assessments (N = 114 for two-year observation). Further, substance use profiles may change over a longer period. Of the total sample, 291 had undergone two consecutive yearly assessments with the full battery of cognitive tests. Further, 252 had valid test data for at least one test at both time points and 236 of those have at least four months of valid substance use data in the year between assessments (Figure 1).

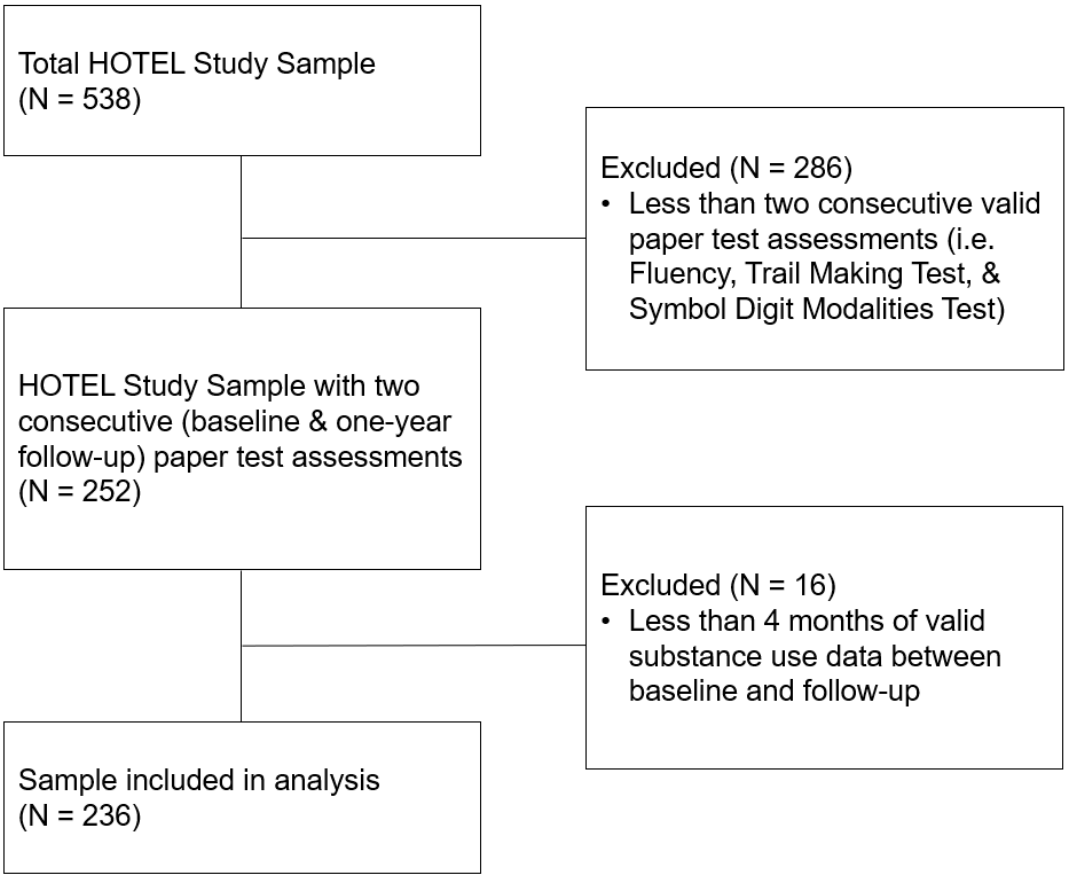

Figure 1. Sample Selection Flowchart

1.2.2. Procedure

Substance use was evaluated monthly using the Time Line Follow Back, which evaluates frequency (days per week), dosage, and cost of all substances used over the past month (TLFB, Sobell, Sobell, Klajner, Pavan, & Basian, 1986). This measure has been evaluated in homeless persons previously and was found to have good test-retest reliability, as well as concurrent validity with other self-report measures and clinician ratings (Sacks et al., 2003). Our sample had a minimum of four observations of the TLFB and a maximum of thirteen (M = 9.41, SD = 2.58). Substance use (TLFB) was validated through regular Urine Drug Screens (UDS). The number of UDS for the four substances (opioids [heroin, morphine, methadone], methamphetamine, cannabis [11-nor- Δ9-tetrahydrocannabinol-9-COOH], cocaine)

over the year ranged from zero to twelve (M = 1.70, SD = 2.31), with 153 participants having at least one UDS over the year of observation. An additional 47 participants had more extensive UDS panels for opioids (i.e. fentanyl, oxycodone, hydromorphone; Supplemental Table 3). In addition to a UDS, acute substance use is collected via a day-of evaluation of substance use in the past 24 to 48 hours prior to cognitive assessment.

Determination of human immunodeficiency virus (HIV), Hepatitis B (HCB), and Hepatitis C (HCV) status is achieved through yearly serology, with qualitative polymerase chain reaction (qPCR) testing for active infection in those with positive HCV serology. Trained research assistants conducted interviews at study entry to assess lifetime history and onset of substance use, in addition to medical history (e.g. TBI, stroke). An experienced psychiatrist (Dr. William G Honer, Dr. Olga Leonova) determined substance use and mental disorder diagnoses using the Best Estimate Clinical Evaluation and Diagnosis (BECED; Endicott, 1988) according to the DSM-IV (American Psychiatric Association, 2000) at study entry. In addition, the Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) was conducted by research assistants on a yearly basis to follow diagnoses over time.

1.2.3. Data Analysis

To address our initial aim of profiling substance use, a two-step cluster analysis (hierarchical and k-means) was run for the average days of use per month for the five major substances over one year. A hierarchical cluster analysis was first employed to determine the appropriate number of clusters using Ward's method (Lange, Iverson, Senior, & Chelune, 2002; Milligan, 1980). Squared Euclidian distance was used as the similarity measure to incorporate profile shape and elevation (Everett, Landau, Leese, & Stahl, 2011; Gicas et al., 2014). Cluster number was evaluated through investigation of dendrograms for natural breaks (Gicas et al., 2014; Lange et al., 2002; Lange, Iverson, & Franzen, 2008). The dataset was split in half at random and the cluster analysis was run on both halves to determine that the same number of clusters was indicated (Fernandez-Calderon et al., 2011; Zimmerman & Maton, 1992).

K-means cluster analysis was run using the indicated number of clusters and random seed points to minimize bias towards the results of the hierarchical analysis (Gicas et al., 2019; Gicas et al., 2014; Lange et al., 2002). Groups were compared on substance use frequency to confirm that substance use across clusters was effectively differentiated (Fernandez-Calderon

et al., 2011). A multi-method multi-profile matrix correlating the profiles across methods was created for internal validation (Fisher et al., 1996; Gicas et al., 2014; Lange et al., 2002).

ANOVA, Kruskal-Wallis H, and Chi Square analyses were used to externally validate the use of substance profiles derived from the self-report TLFB. Groups were compared on relevant measures of substance use behaviour (i.e. urine drug screens, substance dependence diagnoses, viral infection, and intravenous use) to establish convergence across measures across the same period of time. Diagnoses were determined at follow-up (T2) and are based on the preceding year of observation.

To evaluate relevant risk factors and outcomes of polysubstance use, ANOVA and Kruskal-Wallis H tests were used to compare substance use profile groups on age, education, premorbid IQ (Wechsler Test of Adult Reading; Wechsler, 2001). Chi Square and Fisher's exact analyses were used to compare groups on tobacco use, mental health diagnoses (Major Depressive Episode, Generalized Anxiety Disorder [GAD], Post-Traumatic Stress Disorder [PTSD], Manic Episode, Substance-Induced Psychosis, and schizophrenia spectrum disorder), history of TBI, and history of stroke.

In addition, acute use (at T1 and T2) and lifetime history of use (lifetime dependence diagnoses and age of onset of use) were compared across groups to evaluate whether one-year substance use histories were conflated with intoxication, remote or cumulative use, or developmental period of onset of use, which have various implications for cognition and function (Supplemental Table 1).

Given that we did not have prior hypotheses and planned comparisons, we evaluated the null hypotheses that no group differences existed. Post-hoc analyses were conducted for omnibus tests that revealed a significant result, with management of multiple comparisons through Tukey's HSD for ANOVA and Dunn's (1964) Bonferroni procedure for Kruskall-Wallis and Chi Square analyses.

1.3. Results

Cluster analysis revealed three- and five-cluster solutions. The three-cluster solution provided the best convergence across methods, suggesting good internal validity (Table 2). That is, the multi-method multi-profile matrix indicated that the profiles that emerged across both hierarchical and k-means algorithms correlate positively with their respective profiles (e.g. K1

and H1), while noncorresponding profiles (e.g. K1 and H2) demonstrate nonsignificant correlations. Further, the three-cluster solution effectively separated all substances but cocaine (Table 3).

Table 2. Multi-Profile Multi-Method Correlation Matrix

	Hierarchical Analysis (Ward's)			K-Means Analysis		
	H1	H2	H3	K1	K2	K3
H1	1.00					
H2	-0.41	1.00				
H3	-0.33	-0.69	1.00			
K1	1.00**	-0.42	-0.32	1.00		
K2	-0.37	0.97**	-0.63	-0.38	1.00	
K3	-0.34	-0.68	0.93**	-0.32	-0.72	1.00

Note. * = significant at the 0.05 level. ** = significant at the 0.01 level.

Table 3. Median (IQR) Days of Use per Month Across Clusters

Substance	Cluster 1: Frequent Cannabis Use	Cluster 2: Frequent Heroin Use	Cluster 3: Infrequent to Moderate Use
Meth	0.10 (13.95)*	6.00 (18.10)**	0.00 (2.64)
Heroin	0.00 (0.44)	21.88 (12.92)**	0.00 (0.53)
Cocaine	0.00 (4.00)	0.00 (1.83)	0.09 (6.87)
Cannabis	26.00 (5.80)**	1.60 (7.40)	0.10 (1.82)
Alcohol	1.17 (6.87)*	0.25 (0.67)	0.53 (4.24)

Note. N = 246 (Cluster 1[n = 61], Cluster 2 [n = 47], Cluster 3 [n = 128]. Pairwise comparisons used Dunn's (1964) procedure with Bonferroni correction.
** = Significantly ($p < 0.05$) higher than both other groups. * = Significantly ($p < 0.05$) higher than one other group.

We found three prominent substance use profiles in our sample: Infrequent to Moderate Polysubstance Use (n = 128), Frequent Heroin with Moderate Methamphetamine Use (n = 47), and Frequent Cannabis Use (n = 61; Table 3, Figure 2). The moderate group consisted of 63.4% individuals who used substances less than 14 days per month, including 6.3% individuals who did not use any of the five substances in the year of observation. The cannabis profile group was composed of 80.3% persons engaged in frequent cannabis use and 13.1% frequent methamphetamine use. The heroin profile group was composed of 61.7% persons engaged in frequent (22-28 days) heroin use and 19.1% frequent methamphetamine use (see Supplemental Figures 1-5).

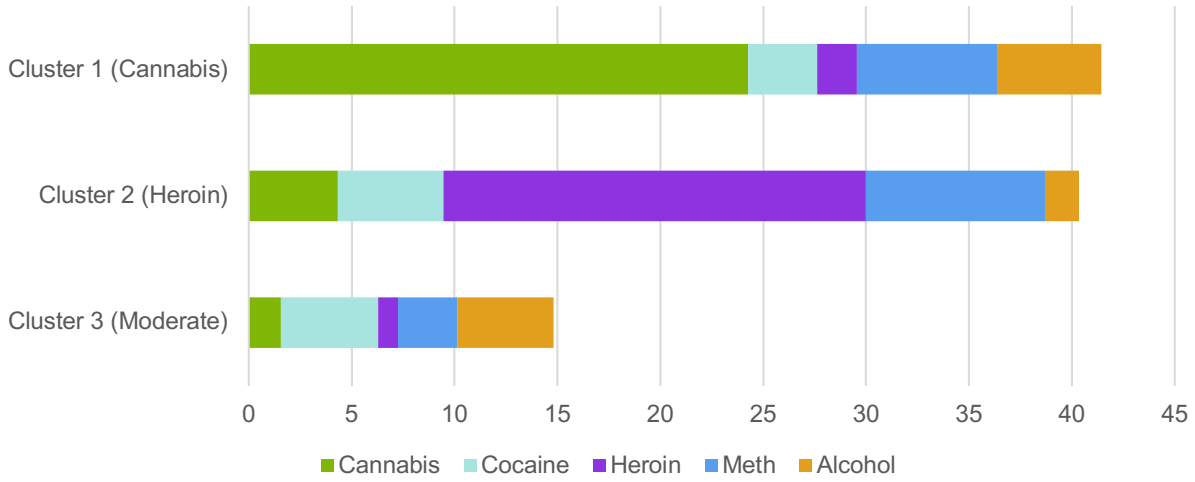

Figure 2. Stacked Bar Graph of Mean Days of Use per Month Across Clusters

Note. Mean number of days of use per month (28 days) of each substance across profile groups. Total bar represents average number of use days per month (maximum of one per day per substance). Given that the mean is more sensitive to outlying values and the frequency of use was not normally distributed, Figure 2 (means) does not perfectly align with Table 3 (medians).

Given the above profiles, we would expect that diagnoses of dependence, acute use, and urine drug screens would follow the frequency of use patterns in Figure 2. Additionally, intravenous use and viral infection would be expected to be more prevalent among the Frequent Heroin Use group. As expected, persons primarily using heroin had elevated rates of intravenous use and HCV, as well as higher rates of positive UDS, acute use, and dependence diagnoses for both heroin and methamphetamine. Similarly, rates of cannabis dependence, acute use, and positive UDS for Δ9-THC were greatest in the Frequent Cannabis Use group. In line with self-reported use, groups did not differ on diagnoses of dependence or UDS for alcohol or cocaine (Table 4). Differences in acute use, age of onset of use, and lifetime diagnoses can be found in Supplemental Table 1 and 2. It is also important to note that while heroin is the most commonly used opioid in our sample and was used to differentiate groups, individuals in the heroin profile group also frequently screen positive for other types of opioids (e.g. fentanyl; Supplemental Table 3).

Table 4. External Validation of Cluster Profiles

Characteristic		Cluster Profile				
		Cannabis (n=61)	Heroin (n=47)	Moderate (n=128)	Test Statistic	Comparison
Dependence†	Alcohol [n=199]	22.0%	4.9%	16.7%	$X^2(2)=5.235$	
	Cocaine [n=201]	27.5%	16.7%	33.3%	$X^2(2)=4.162$	
	Cannabis** [n=202]	80.4%	9.3%	8.3%	$X^2(2)=100.311$	C>H, C>M
	Heroin** [n=201]	15.7%	90.5%	17.6%	$X^2(2)=82.075$	H>M, H>C
	Meth* [n=201]	29.4%	50.0%	25.0%	$X^2(2)=8.901$	H>M, H>C
Intravenous Use	IV use during observation year**	45.9%	100.0%	53.9%	$X^2(2)=38.608$	H>M, H>C
Viral Infection	HIV [n=217]	14.5%	16.3%	17.6%	$X^2(2)=0.265$	
	Hepatitis B [n=213]	30.9%	26.8%	38.5%	$X^2(2)=2.196$	
	Hepatitis C* [n=213]	36.4%	63.4%	43.9%	$X^2(2)=7.055$	H>C
% Positive UDS	Cocaine, *Med (IQR)* [n=155]	0.00 (1.00)	0.22 (0.83)	0.00 (1.00)	*H*=0.532	
	Δ9-THC, *Med (IQR)*** [n=154]	1.00 (0.00)	0.50 (1.00)	0.00 (0.50)	*H*=57.771	C>H, C>M, H>M
	Opioid, *Med (IQR)*** [n=147]	0.00 (1.00)	1.00 (0.22)	0.58 (1.00)	*H*=23.290	H>C, H>M
	Meth, *Med (IQR)*** [n=155]	0.00 (1.00)	1.00 (0.42)	0.00 (1.00)	*H*=14.197	H>C, H>M

Note. N = 236, unless otherwise specified.

† Diagnoses based on the Mini International Neuropsychiatric Interview closest to one-year follow-up (Within 275 days, M = 41.96 days, SD = 47.75). *Significant to $p < 0.05$. **Significant to $p < 0.01$.

Our investigation of risk factors and outcomes of polysubstance use profiles indicated that groups differed in age, such that the moderate use group was older than the cannabis and heroin use group. Additionally, the heroin use group had elevated rates of Major Depressive Episode (MDE). Analysis did not reveal statistically significant differences across substance use profiles in gender; ethnicity; premorbid IQ; years of education; baseline tobacco use, history of self-reported traumatic brain injuries resulting in loss of consciousness; stroke; or diagnoses at the one-year follow-up of Manic Episode, PTSD, GAD, psychotic disorder, or substance-induced psychosis (Table 5).

Table 5. Demographics and Comorbidities Across Profile Groups

Characteristic		Cluster Profile				
		Cannabis (n=61)	**Heroin (n=47)**	**Moderate (n=128)**	**Test Statistic**	**Effect size (Comparison)**
Demographics	Age (years), *M (SD)**	43.13 (12.68)	38.82 (10.96)	47.80 (11.60)	$F_{2,233}$=10.839	*d*=0.76 (M>H), *d*=0.38 (M>C)
	Education years, *Med (IQR)*	10.00 (2.00)	10.00 (3.00)	10.00 (3.00)	*H*=1.865	
	Premorbid IQ (WTAR), *M (SD)* [n=222]	99.11 (7.24)	98.29 (7.75)	98.55 (9.92)	$F_{2,219}$=0.118	
	Gender (% Female)▲	16.4%	30.4%	25.0%	$X^2(2)$=3.061	
Substance Use	Baseline daily use of tobacco [n=230]	78.3%	93.5%	80.6%	$X^2(2)$=4.879	
Diagnoses†	Major Depressive Episode** [n=197]	20.0%	35.0%	8.4%	$X^2(2)$=15.268	*OR*=5.86 (H>M), *OR*=2.72 (C>M)
	Generalized Anxiety Disorder [n=200]	13.5%	0.0%	8.4%	*p*=0.099	
	Manic Episode [n=198]	10.0%	4.7%	7.6%	*p*=0.675	
	PTSD [n=197]	16.0%	11.9%	6.7%	*p*=0.178	
	Substance-Induced Psychosis [n=184]	6.3%	14.7%	8.8%	*p*=0.475	
	Psychotic Disorder□ [n=196]	37.3%	48.7%	30.2%	$X^2(2)$=4.335	
Neurological Health	TBI with LOC	32.8%	27.7%	33.6%	$X^2(2)$=0.567	
	Stroke [n=230]	3.3%	4.5%	4.0%	*p*=1.00	

Note. N = 236, unless otherwise specified. Effect sizes were calculated for each significant pairwise comparison (*d* [mean difference/pooled standard deviation] for ANOVA with medium effect = 0.5, Cohen, 1992 and odds ratio for Chi-square).

† Diagnoses based on the Mini International Neuropsychiatric Interview closest to T2 (Within 275 days of T2, M = 41.96 days, SD = 47.75). ▲ = One individual who identified as transgender was not included in the Chi Square analysis of gender. □ = Schizophrenia, schizoaffective, and psychotic disorder not otherwise specified. *Significant to $p < 0.05$. **Significant to $p < 0.01$.

1.4. Discussion

To our knowledge, this is the first study to identify, characterize, and validate polysubstance use profiles among homeless and precariously housed individuals. We improve upon past work by prospectively sampling substance use and validating self-reported use through urine drug screen and clinician diagnoses. Further, we did not select the sample based on substances of choice. The prevalence of substance use in this sample (Vila-Rodrgiguez et al., 2013) allowed us to establish distinct and robust profiles of use among individuals who are similar in terms of sociodemographics and environment, allowing for comparison across divergent polysubstance use profiles.

Cluster analysis revealed that groups were primarily separated on their use of heroin and cannabis, resulting in a Frequent Heroin with Moderate Methamphetamine Use, a Frequent Cannabis Use, and an Infrequent to Moderate Polysubstance Use group. These groups are consistent with preliminary analyses and past work that has established that methamphetamine use and both heroin and cannabis use often co-occur, while the combined use of methamphetamine and cocaine use, as well as alcohol and heroin use is less common. This is consistent with a general pattern of mixing stimulants and depressants (Bolla, Funderburk, & Cadet, 2000; Chen, Wang, Lin & Chen, 2015; Horner, 1997; Leri, Bruneau, & Stewart, 2002; Patra, Fischer, Maksimowska, & Rehm, 2009). The profile groups we found also support recent longitudinal findings that cannabis use is associated with less illicit opioid use among individuals with chronic pain (Lake et al., 2019). Surprisingly, the majority of the sample fell into the moderate use group. This may represent a heterogeneous group with respect to drugs of choice and to recent and remote histories. However, this group provides a comparison with respect to the two key profiles that emerged (heroin and cannabis). While many profiles could have been extracted, this study has established that this population may be best differentiated in their substance use behaviours based on their frequency of heroin and cannabis use.

Importantly, cluster profiles were externally validated by comparing groups on separate measures of substance use behaviour, including objective measures of substance use (i.e. percent positive and day-of evaluation urine drug screens), clinician diagnoses of dependence according to the BECED and the MINI, self-reported acute use at cognitive evaluation, and rates of associated health outcomes (e.g. viral infection). Differences in rates of HCV are consistent

with the rates of intravenous administration among the heroin use group in this study, as expected (Bell et al., 1990). As such, the TLFB was found to be useful in monitoring daily substance use among precariously housed persons and our cluster analysis revealed meaningful profiles. Further, understanding group differences in acute use patterns, history of substance use, and viral infection can provide a more thorough understanding of differences across groups in cognitive and everyday functioning.

Evaluation of potential risk factors and outcomes associated with substance use profile groups revealed that the moderate use group was older than the frequent use groups, which may be due to some of the older participants reducing their overall substance use with age. Past work indicates a decline in use with age in the general young adult population (Kandel & Logan, 1984; O'Malley, Bachman, & Johnston, 1984) and we found similar rates of lifetime dependence diagnoses across substance use profile groups in our study (i.e. persons in the Infrequent to Moderate Use group may have met criteria previously; Supplemental Table 1). By comparison, younger age may be a risk factor for increased frequency of substance use. We also found higher rates of MDE among the frequent use groups, which could represent a risk factor and/or a consequence of use (Sullivan, 2018). It may be indicative of a self-medication strategy (McKernan et al., 2015; Weiss, Griffin, & Mirin, 2009) or could represent an overlap or exacerbation of symptoms of depression among persons engaged in frequent use, for example during withdrawal from heroin (Powell & Taylor, 1991).

These profiles of substance use can be used to identify and target differential needs of use groups. This is particularly important given the lack of prevention and treatment approaches for polysubstance use relative to single substance use and abuse (Connors, Gullo, White, & Kelly, 2014; Patra, Fischer, Maksimoska, & Rehm, 2009). An important next step is determining whether these groups differ in cognitive and functional outcomes. Given past work highlighting the negative neurocognitive consequences of HCV and depression among women with HIV (Giesbrecht et al., 2014), these factors, along with age, will be considered in subsequent analyses and interpretation of results of Study 2.

Study 2

2.1. Introduction

Chronic substance use is known to have negative effects on cognitive function. These effects typically wane with abstinence, though long-term difficulties and structural brain changes may be seen following chronic use of any of the major substances (Rocchetti et al., 2013; Thompson et al., 2004; Walker, Hunter, & Abraham, 1981; Wollman et al., 2017). There is an abundance of literature on the neuropsychological effects of each substance. Table 6 summarizes the cognitive impairments associated with chronic use of substances (i.e. substance use disorder) relative to healthy controls or a minimal use group (cannabis) from existent meta-analyses (Potvin et al., 2018; Potvin, Stavro, Rizkallah, & Pelletier, 2014; Scott et al., 2018; Stavro, Pelletrier, & Potvin, 2012; Wollman et al., 2019).

Table 6. Summary of Effect Sizes for Chronic Use of Substances of Interest on Cognition

		Alcohol	Opioids	Meth	Cocaine	Cannabis
Study characteristics	**Abstinence**	0 to 31 days	>3 months	4.5 months (M)	≤12 weeks	0 to 152.7 hours
Cognitive domains	**IQ/Global**	0.33		0.46		
	Language/ Fluency	0.40	0.32	0.43	0.22	
	Attention		0.57			0.21
	Processing speed	0.47	0.24	0.34	0.45	0.26
	Working memory	0.53	0.77	0.51	0.52	0.22
	Executive function	0.53	0.42	0.49	0.59	0.30
	Verbal learning	0.45	0.56	0.28	0.45	0.33
	Verbal memory	0.38	0.60	0.40	0.56	0.26
	Impulsivity	0.46	0.41	0.93	0.58	0.25

Note. Effect sizes are standardized mean difference statistics (*d*) that were weighted and pooled (Hedge's g). Estimates are based on a minimum of five studies and studies with the smallest duration of abstinence. Please see the referenced studies for a more thorough summary of effect sizes for different durations of abstinence (Potvin et al., 2018; Potvin, Stavro, Rizkallah, & Pelletier, 2014; Scott et al., 2018; Stavro, Pelletrier, & Potvin, 2012; Wollman et al., 2019).

The five substances above are associated with a broad range of standardized mean-difference effects across domains of cognition. Despite shorter durations of abstinence, regular cannabis use has relatively small effects (Scott et al., 2018), while opioids and

methamphetamine, with relatively longer durations of abstinence, show small to moderate effects (Potvin et al., 2018; Wollman et al., 2019). Further, Table 6 provides preliminary evidence that substances may have both shared and differential effects for particular cognitive skills. For example, methamphetamine use may be more strongly related to greater impulsivity and less so to diminished verbal learning (Potvin et al., 2018; Scott et al., 2007).

According to the results of Study 1, the primary substances differentiating individuals in our sample are heroin, cannabis, and methamphetamine. These three substances have both overlapping and contrasting neurocognitive patterns associated with their regular use (Lundqvist, 2005; Ornstein et al., 2000). Past work has suggested that chronic opioid use is not associated with frontal lobe deficits (Hill, Reyes, Mikhael, & Ayre, 1979; Rogers & Robbins, 2001), while other have suggested that chronic heroin use appears to cause damage to the prefrontal cortex, but not the frontostriatal loop (Kosten & George, 2002). Others have found that regular use of opiates appears to selectively disrupt brain metabolism in the temporal cortex (Moreno-Lopez et al., 2012), which is consistent with neuropsychological findings of domain-specific impairment in learning and memory among persons who use opioids (Arias et al., 2016). In contrast, chronic methamphetamine use is most consistently associated with deficits in working memory, attention, and executive function due to the dopaminergic frontostriatal and thalamocortical pathways that are sensitive to methamphetamine neurotoxicity (Barr et al., 2006). Chronic methamphetamine use has also been implicated in deficits in verbal memory, which may be due to the neurotoxic effects of methamphetamine on norepinephrine and serotonin terminals in the hippocampus (Barr et al., 2006). Further, heroin and methampethamine used together may be more neurotoxic than either alone (Tian et al., 2017), which is a common pattern of use among the heroin use cluster group. Regular cannabis use has been associated with structural abnormalities in the hippocampus and associated regions which are dense in cannabinoid receptors (Rocchetti et al., 2013; Yucel et al., 2008; Zalesky et al., 2012), though cognitive deficits have been found for attention and executive function in addition to episodic memory (Crean, Crane, & Mason, 2011; Scott et al., 2018). As such, while combinations of these substances likely result in global network dysfunction, the three substances may result in more or less disruption of frontal and temporal networks underlying distinct cognitive functions (Lundqvist, 2005).

Not only does chronic use of substances have additive negative consequences (e.g. alcohol and cocaine each have dose-related associations with cognition that increase when used together; Bolla, Funderburk, & Cadet, 2000), but substances also interact with each other

in ways that are not fully understood, particularly as they relate to cognition. The reported impact of methamphetamine on cognition has been positively (Castelli et al., 2014) and negatively (Cuzen et al., 2015) modified by cannabis use, while other studies show no moderation (Gonzalez et al., 2004). While some cognitive domains may be particularly sensitive to certain substances (e.g. alcohol and stimulants on impulsivity and flexibility), other domains (e.g. decision-making) are similarly impacted regardless of the substances used (Fernandez-Serrano, Perez-Garcia, and Verdejo, 2011)[1].

While research highlighting the effects of single substances is helpful to guide our understanding of the affected neural networks, profiling use patterns is a useful way to study the cognitive effects of polysubstance use that we might expect in clinical practice. One study has previously investigated the relationship between cognition and polysubstance use profiles, finding that use profiles differed in demographic factors and that those associated with older age and less education (e.g. polysubstance use groups) tended to perform worse than those younger and had more education (e.g. multi-injection and nasal heroin use; Harrell et al., 2014). Importantly, demographics and comorbidities differentially associated with use profiles can help clarify relevant contributors to cognitive and functional outcomes.

Cognitive impairment is common among homeless adults, with an estimated frequency of 25% according to quantitative review (Depp, Vella, Orff, & Twamley, 2015). Risk factors for impairment are varied given the multimorbidity in this population. Polysubstance use is associated with a host of comorbidities, including HCV (Bell et al., 1990) and mood disorders (Khan, 2017; Quello, Brady, & Sonne, 2005), both of which have been implicated in neurocognitive functioning (Giesbrecht et al., 2014). Study 1 revealed that the Frequent Heroin with Moderate Methamphetamine Use and Frequent Cannabis Use groups had elevated rates of major depressive episode. This is consistent with past work linking symptoms of depression and opioid use (Goesling et al., 2015). Further, concurrent mood and substance use disorders are associated poorer prognosis, including treatment resistance and increased hospitalization (Quello, Brady, & Sonne, 2005).

Taken together, substance use and associated comorbidities are associated with functional impairment and disability (Crouse et al., 2019) and greater difficulty engaging in with social support and services that may contribute to exiting homelessness (Zlotncik, Tam, &

[1] For a systematic review of specific and general effects of substance use at various lengths of abstinence see Fernandez-Serrano, Perez-Garcia, and Verdejo, 2011).

Robertson, 2003). Persons in the community who are engaged in chronic substance use have also been found to report greater difficulty with social, occupational, and physical functioning compared to treatment seekers (Eland-Goossensen, van de Goor, & Garretsen, 1997). Substances differ in their functional impact, particularly given the relative risks of physical dependence and overdose. Opioids are associated with elevated risk of dependence, overdose, and physical disability (e.g. chronic pain, viral infection). Unlike opioids, withdrawal and relapse are non-lethal in cannabis, which has been used to suggest cannabis as a treatment for opioid use disorder (Wiese & Wilson-Poe, 2018).

Study 2 Aim 1 (Cognition): To ascertain whether one-year cognitive change trajectories and cognitive capacity vary across polysubstance use profiles. *Study 2 Aim 1 (Cognition) Hypotheses:* The Moderate Use profile group was expected to have the smallest decline and best overall performance on cognitive testing, particularly for processing speed given that this group has the lowest exposure to multiple substances with known lasting cognitive effects (Fernandez et al., 2011). In contrast, the frequent heroin use group was expected to have the poorest performance, given the burden of comorbidities and past neuropsychological (Arias et al., 2016; Fernandez et al., 2011) and brain imaging (Moreno-Lopez et al., 2012) findings. *Study 2 Aim 1a:* To investigate the role of variables that differ across profile groups (i.e. age, HCV, depression) in cognitive outcomes.

Study 2 Aim 2 (Function): To explore whether differences exist across polysubstance use profiles in role, social, and occupational functioning. *Study 2 Aim 2 (Function) Hypothesis:* Function was expected to follow a similar pattern to cognition, such that the moderate use group was expected to be the highest functioning and the heroin use group was expected to have the poorest overall function. *Study 2 Aim 2a:* To investigate the role of variables that differ across profile groups (i.e. age, HCV, depression) in functional outcomes.

2.2. Method

2.2.1. Participants

Study 2 included the same sample as Study 1 (see Figure 1 and Table 1). Given our sample size of 236, power was determined to be adequate to achieve the stated aims of this study based on expected effect sizes for between subject and within subject differences in cognition as discussed above (Table 6; Appendix A).

2.2.2. Procedure

Cognition was assessed on a yearly basis as part of the larger, ongoing longitudinal HOTEL study. Assessments were completed by trained research assistants under the supervision of a clinical neuropsychologist (full battery in Appendix B). Measures were chosen to represent a wide range of neurocognitive abilities known to be sensitive to a variety of neurological insults (e.g. substance use, TBI, viral infection). Given the clusters obtained in Study 1 (Heroin, Cannabis, Moderate), we aimed to investigate domains that have been found to be sensitive to chronic use of heroin, cannabis, and methamphetamine. We aimed to have measures sensitive to processing speed, attention, and executive function, in addition to measures sensitive to verbal memory. Further, given that we are interested in cognitive change over time, we selected measures with good test-retest reliability (Appendix B).

Assessments included both paper and pencil tests, as well as computerized tests from the *Cambridge Neuropsychological Test Automated Battery* (CANTAB). Computerized tests included a measure of sustained attention for visual information (Rapid Visual Information Processing, CANTAB-RVP) and an analogue of the Wisconsin Card Sorting test to evaluate cognitive flexibility and reversal learning (Intra-Extra Dimensional Set Shift subtest, CANTAB-IED; Fray, Robbins, & Sahakian, 1996). Processing speed with executive control was evaluated with the Symbol Digit Modalities Test (SMDT; Smith, 1973), the Trail Making Test (TMT; Reitan, 1958), the Stroop test (Golden & Freshwater, 1978), and the Controlled Oral Word Association Test (COWAT; Benton, Hamsher, & Sivan, 1983). The SDMT is a substitution task requiring working memory of symbols, while the TMT involves sequencing and flexibility, and the Stroop test involves response inhibition for reading coloured words. Finally, verbal memory was assessed using the revised Hopkin's Verbal Learning Test of word list learning (HVLT-R; Brandt & Benedict, 2001).

Each measure has been well validated for use in a variety of populations (Dickinson, Ramsey, & Gold, 2007; Fray, Robbins, & Sahakian, 1996; Golden & Freshwater, 1978; Barry & Petry, 2008; Lezak, Howieson, Bigler, & Tranel, 2012; Lowe & Rabbitt, 1998; Reitan, 1958; Ross et al., 2007; Shapiro, Benedict, Schretlen, & Brandt, 1999; Smith, Need, Cirulli, Chiba-Falek, & Attix, 2013) and has good test-retest reliability (Benedict et al., 2012; Benedict, Schretlen, Groninger, & Brandt, 1998; Dikmen, Heaton, Grant, & Temkin, 1998; Goncalves, Pinho, & Simoes, 2015; Koh et al., 2011; Lezak, Howieson, Bigler, & Tranel, 2012; O'Neill-Pirozzi, Goldstein, Strangman, & Glenn, 2011; Pereira, Costa, & Cerqueira, 2015; see Appendix

B). Finally, each of the paper measures has been previously used to assess cognition in homeless individuals with multimorbidity (Barone et al., 2019; Foulks, McCown, Duckworth, & Sutker, 1990; Gabrielian et al., 2015; Gonzalez, Dieter, Natale, & Tanner, 2001; Stergiopoulos et al., 2019).

Overall functioning in a variety of domains (social, occupational, self-care, health) was evaluated every six months using the Role Functioning Scale (RFS; Goodman, Sewell, Cooley, & Leavitt, 1993). The Global Assessment of Functioning (GAF) scale is also done every six months and is a scale from 1 (severely impaired) to 100 (extremely high functioning) from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR; American Psychiatric Association, 2000). This includes the Social and Occupation Functioning Assessment Scale (SOFAS; Goldman, Skodol, & Lave, 1992). Both scales are interviewer-rated. Raw scores on the SOFAS ranged in the sample from 15 (Some danger of hurting self or others, failure to maintain minimal personal hygiene, or gross impairment in communication) to 90 (Absent or minimal symptoms, good functioning in all areas). Scores from 30 to 50 indicate serious or major impairment in one or more areas of social and occupational functioning.

In addition to yearly diagnostic interviews, depressive symptoms are monitored monthly using the Beck Depression Inventory (BDI-II; Beck, Steer, & Brown, 1996). The BDI-II has a one-week test-retest reliability of $r = 0.93$ and an internal consistency of $\alpha = 0.91$ (Beck, Steer, & Brown, 1996).

2.2.3. Data Analysis

A subset of the cognitive measures had substantial missing data. Little's Missing Completely at Random test was significant ($p = 0.023$), suggesting that the cognitive data is not missing completely at random. Missingness in these measures can be explained by procedural changes that differentially affected each cohort and each test (e.g. newer recruits stopped undergoing computer-based tests, inability to do the task for TMT B). The variables with large amounts of missing data (Bennet, 2001) were correlated with other complete variables. As such, these measures (IED, RVP, SDMT, TMT B) were dropped (Tabachnick & Fidell, 2012; Appendix C).

To minimize redundancy, the remaining measures were conceptualized into two cognitive domains: Processing Speed with Executive Control and Verbal Memory. Past neuropsychological and brain imaging work has differentiated processing speed and executive functioning from learning and memory (Chiaravalloti, Christodoulou, Demaree, & DeLuca, 2003; King & Anderson, 2018). These two factors allow us to evaluate two potentially contrasting neural networks which could be differentially affected by various substance use patterns. Namely, the Processing Speed/Executive Control measures (e.g. FAS, Stroop) likely recruit more frontal brain areas (Kochunov et al., 2010), while the Verbal Memory measures likely recruit more temporal areas (e.g. HVLT delay and recognition; Bonner-Jackson, Mahmoud, Miller, & Banks, 2015; Squire, Wixted, & Clark, 2007).

Raw scores were converted to standardized scores (Z-scores) for comparison across measures. Raw TMT A scores were transformed (multiplied by negative one) to ensure that higher scores were associated with greater performance. Z-scores were computed using the sample's baseline mean and standard deviation, allowing us to compare change in scores over time. This further allowed us to determine how individuals performed relative to the overall sample. Though it has been argued that you may lose information if the entire sample's scores fall at the low or high end of the measures (Moeller, 2015), our sample displays a broad range of performance and many of the measures do not have minimum and maximum scores (e.g. Stroop, Appendix D). The timed tests (FAS, Animals, Stroop, TMT A) were combined to make a composite measure of Processing Speed/Executive Control. HVLT delayed recall and HVLT recognition were combined to make a composite measure of Verbal Memory. Of the total sample, 82.6% had all four Processing Speed/Executive Control measures at baseline and 80.1% had all four at follow-up. Analyses were completed for the full dataset (i.e. at least one cognitive measure) in addition to only composites with a minimum of two tests at each time point to ensure that results were not biased due to a single measure estimate of cognition.

To address the primary hypothesis about cognitive change and capacity, we employed a 3 x 2 mixed general linear model analysis. In other words, we tested the within-between interaction effects of time (Within-subjects IV) and substance use cluster profile (Between-subjects IV) on cognition (DV). This allowed us to investigate group differences in cognition, while accounting for stable individual factors (e.g. substance use history, demographics, diagnoses). The Processing Speed/Executive Control composite had several (six at T1, eight at T2) outliers as identified by Boxplot inspection (values greater than 1.5 box-lengths). To reduce the impact of these extreme scores, outliers were pulled in to the next highest or lowest value

while maintaining order (Tabachnick & Fidell, 2012). With this adjustment, data fell on a normal distribution. Homogeneity of variances was violated ($p = 0.011$) at T1, so an alpha of $p < 0.025$ was used to mitigate the potential inflation of type I error (Tabachnick & Fidell, 2012). Box's M test ($p = 0.017$) was within acceptable limits (Tabachnick & Fidell, 2012). The Verbal Memory composite had one outlier at T1 and T2 and was similarly adjusted. Following this adjustment, assumptions (Levene's test $p = 0.104$, $p = 0.115$; Box's M test $p = 0.444$) were met.

To evaluate differences across use profiles in functional change and functional capacity, we again employed a 3 x 2 mixed general linear model analysis. That is, we tested the within-between interaction effects of time (Within-subjects IV) and substance use cluster profile (Between-subjects IV) on function (DV). Overall functioning (psychological, work, social, and self-care) was evaluated by the RFS and SOFAS at baseline and one-year follow-up. RFS violated assumptions of normality and homogeneity of variance and covariance. SOFAS had a better distribution for our analysis (i.e. did not violate assumptions). Given the correlation between the two measures ($r = 0.65$-0.75), SOFAS was used as the measure of function. SOFAS also had several outliers (ten at T1, one at T2) that were adjusted as detailed for cognition above. Following adjustments, assumptions (Levene's test T1 $p = 0.200$, T2 $p = 0.319$; Box's M test $p = 0.192$) were met.

2.3. Results

Contrary to hypothesis, rates of change in Processing Speed/Executive Control and Verbal Memory were not significantly different across polysubstance use profile groups ($p = 0.213$ & $p = 0.973$, respectively). Individuals did not differ across substance use profile groups in Verbal Memory or Processing Speed/Executive Control ($p = 0.085$ & $p = 0.154$, respectively), nor did they exhibit change in these abilities over time ($p = 0.427$ & $p = 0.457$, respectively; Figure 3 & 4, Table 7). In other words, groups did not change in cognition over one-year and there were no significant differences in cognition at baseline or one-year follow-up across substance profile groups.

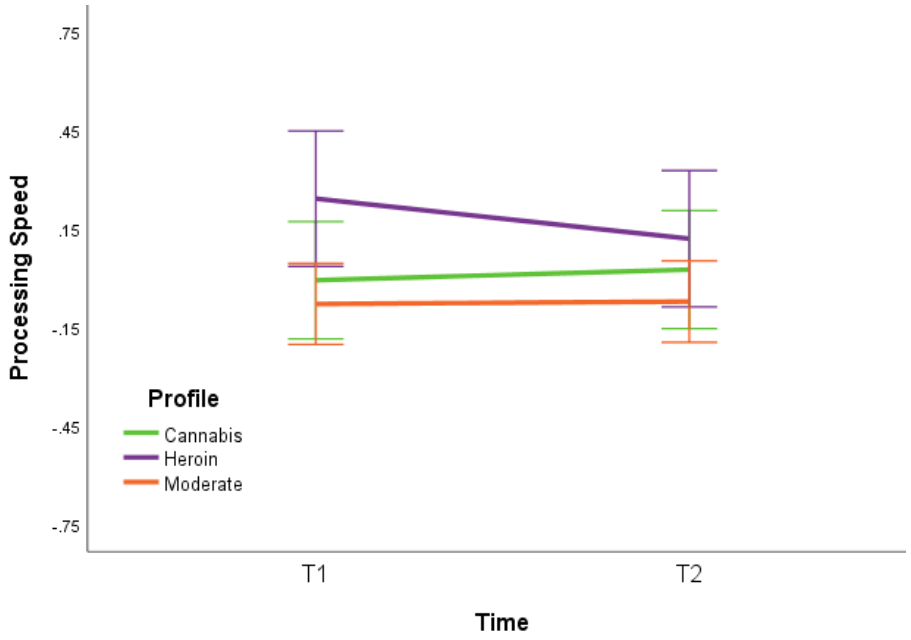

Figure 3. Line Graph of Mean Z-scores on Processing Speed/Executive Control Across Time and Cluster Group

Note. Scale is from 0.75 standard deviations below and above the mean of the sample baseline scores. Scores adjusted for significant outliers. Errors bars: 95% Confidence Interval.

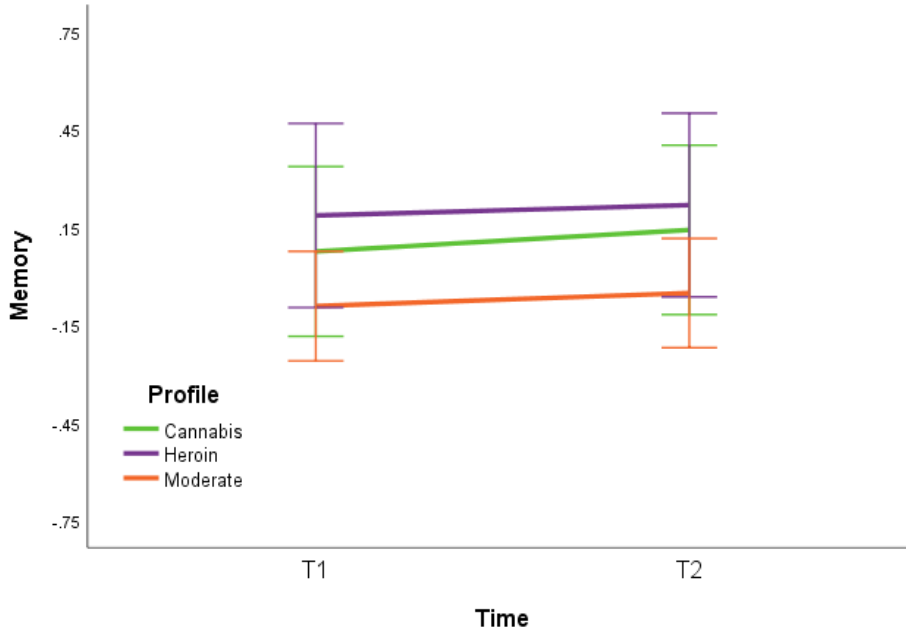

Figure 4. Line Graph of Mean Z-scores on Memory Across Time and Cluster Group

Note. Scale is from 0.75 standard deviations below and above the mean of the sample baseline scores. Scores adjusted for significant outliers. Errors bars: 95% Confidence Interval.

As established in Study 1, groups differed in HCV, MDE, and age. As such, we further investigated the role of these factors in cognitive functioning across profile groups. HCV was not significantly related to Processing Speed/Executive Control (r_{pb} = -0.025, p = 0.715) or Verbal Memory (r_{pb} = -0.083, p = 0.243). Baseline MDE was also not significantly related to Processing Speed/Executive Control (r_{pb} = 0.021, p = 0.752) or Verbal Memory (MDE r_{pb} = 0.048, p = 0.481). Severity of symptoms on the BDI-II at baseline was also not significantly related to processing speed (r_s = 0.122, p = 0.062) or memory (r_s = 0.041, p = 0.550). Increased age was associated with poorer baseline processing speed (r = -0.241, p < 0.001) and memory (r = -0.222, p = 0.001). The main results remained the same (i.e. no interaction or main effects) when accounting for age, which exerted a main effect on Processing Speed/Executive Control ($F_{1,227}$ = 10.839, p = 0.001) and Verbal Memory ($F_{1,196}$ = 5.508, p = 0.020), but did not interact with time (i.e. rate of one-year cognitive change did not relate to age; Processing Speed/Executive Control $F_{2,225}$ = 0.603, p = 0.548; Verbal Memory $F_{2,194}$ =1.197, p = 0.304).

Consistent with hypothesis, profile groups differed in social and occupational functioning ($F_{2,218}$ = 6.320, p = 0.002), such that the Frequent Heroin with Moderate Methamphetamine and Frequent Cannabis Use groups displayed poorer functioning compared to the moderate use group (p < 0.01; Supplemental Table 4). Though differences in functional change were not significant (p = 0.709), groups got slightly better over time at roughly the same rate (p = 0.046; Table 7, Figure 5).

Table 7. Mixed General Linear Model Results for Cluster Profile and Time on Cognition and Function

Measure	Time * Cluster Interaction	Within-Subjects (Time)	Between-Subjects (Cluster)
Processing Speed/ Executive Control	$F_{2,228}$ = 1.557, p = 0.213	$F_{1,228}$ = 0.633, p = 0.427	$F_{2,228}$ = 2.489, p = 0.085
Verbal Memory	$F_{2,198}$ = 0.027, p = 0.973	$F_{1,198}$ = 0.555, p = 0.457	$F_{2,198}$ = 1.889, p = 0.154
SOFAS	$F_{2,218}$ = 0.345, p = 0.709	$F_{1,218}$ = 4.009, p = 0.046*	$F_{2,218}$ = 6.320, p = 0.002**

Note. ** Significant to p < .01. * Significant to p < .05.

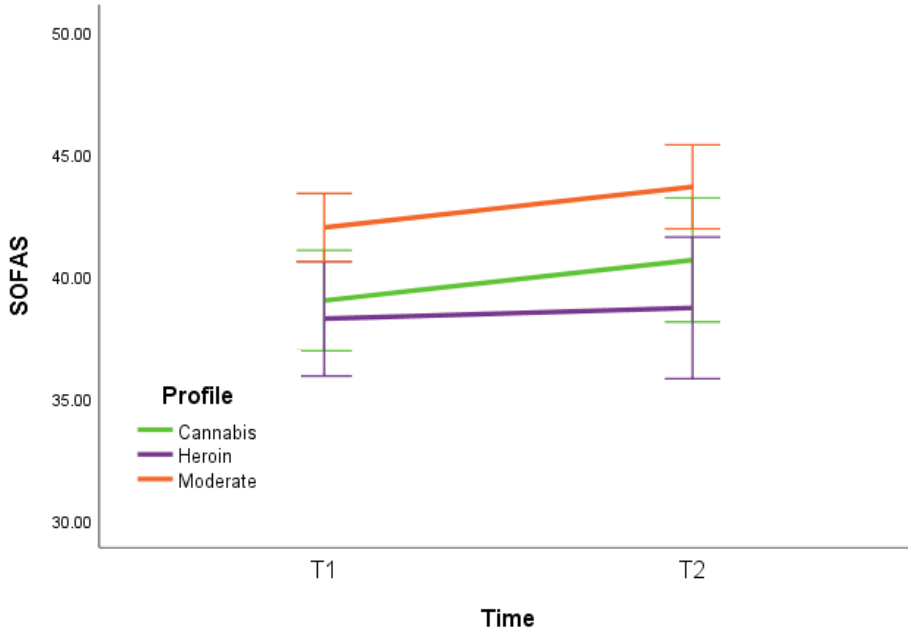

Figure 5. Line Graph of Mean SOFAS Scores Across Time and Cluster Group
Note. Mean is based on raw scores on SOFAS (0 – 100) adjusted for significant outliers. Errors bars: 95% Confidence Interval.

Relevant risk factors and consequences established in Study 1 were again investigated with respect to function. Age (r = 0.11, p = 0.094) and HCV (r = -0.13, p = 0.060) were not significantly related to baseline functioning. Baseline MDE was related to function (r_{pb} = -0.203, p = 0.002). However, change in depression (i.e. depression at T1 only, T2 only, T1 and T2, or neither T1 nor T2) was not associated with change in function (i.e. SOFAS change scores, $F_{3,181}$ = 0.895, p = 0.445). As such, improvement in function does not appear to be explained by change in depressive status. Further, MDE does not appear to explain the poorer functioning among the Frequent Heroin with Moderate Methamphetamine Use group (Figure 6).

To further follow-up on the potential role of depressive symptoms in social and occupational functioning, we conducted an analysis of symptom ratings on the BDI-II. Severity of BDI-II symptom ratings related to function at both baseline (r_s = -0.187, p = 0.005) and follow-up (r_s = -0.147, p = 0.028). The difference in BDI ratings at baseline (Med = 9.00, IQR = 15.00) and follow-up (Med = 7.00, IQR = 16.00) was not significant (Z = 1.038, p = 0.299). As such, the average BDI ratings from the two assessments was added to the main analysis as a covariate. Depressive symptoms (average BDI) interacted with cluster group ($F_{2,215}$ = 3.202, p = 0.043), such that BDI ratings did not relate with functioning in the Frequent Heroin Use (r = -0.204, p = 0.118) and Frequent Cannabis Use (r = -0.068, p = 0.660) groups, while higher levels of

depressive symptoms are associated with lower levels of social and occupational functioning in the Infrequent to Moderate Polysubstance Use group (r = -0.307, p = 0.001). In other words, depressive symptoms do not appear to explain functioning among frequent use groups. Further, the main effect of cluster group on functioning remained significant ($F_{2,215}$ = 7.963, p < 0.001), again suggesting that group differences in function are not explained by depressive symptoms.

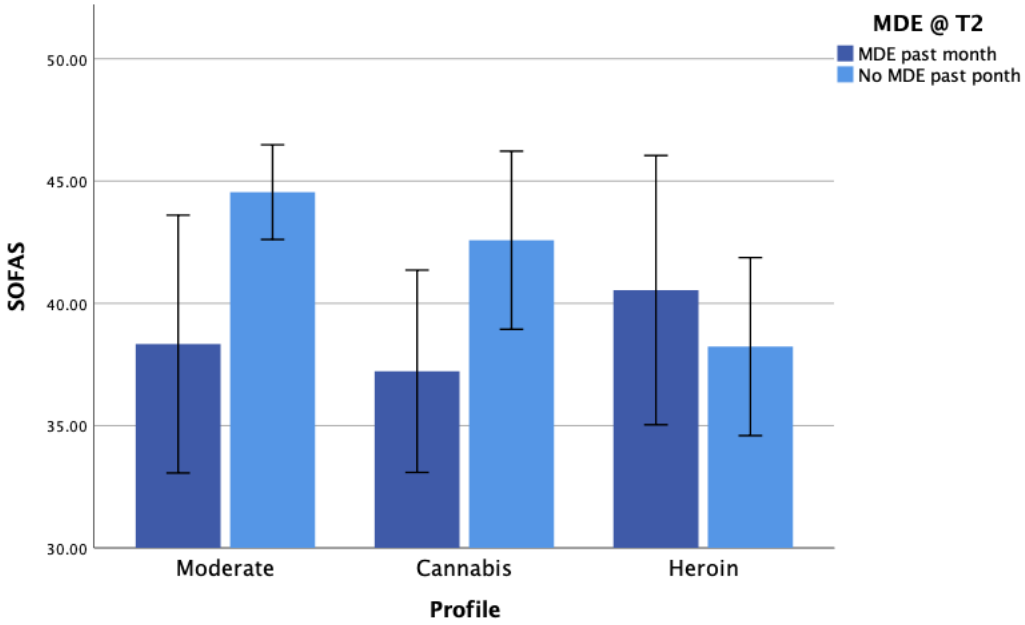

Figure 6. Bar Chart of Mean Function by Cluster Profile and Major Depressive Episode

Note. Mean is based on raw scores on SOFAS (0 – 100). Errors bars: 95% Confidence Interval.

2.4. Discussion

Our results did not suggest differences in cognition across substance use profiles over time, contrary to expectations based on past work establishing the cognitive consequences of substance use (Chen, Wang, Lin, & Chen, 2015; Fernandez et al., 2011). It may be that various substance use patterns have a similar, very small effect (i.e. less than f = 0.09) on cognition over time or that the major use profiles do not have a significant effect on cognition among individuals with extensive use histories over one year. Repeat cognitive testing is associated with improvement in performance (i.e. practice effects). One-year practice effects for our cognitive measures are expected to be small based on a healthy older adult population

(Appendix A). Given that we did not find a change in cognitive performance over one year, this could also indicate cognitive decline approximately equivalent to practice effects.

Surprisingly, cognition did not differ across profile groups at either time point, suggesting that recent substance use did not seem to explain differences in Processing Speed/Executive Control or Verbal Memory in this population. These findings also apply to acute use of substances given that 24- to 48-hour use also differed in accordance with cluster profile group (Supplemental Table 2). Given the differential mechanisms of action and past work showing differences in cognitive profiles associated with heroin and cannabis use (Lundqvist, 2005), we would potentially expect to see a divergence in Processing Speed/Executive Control and Verbal Memory abilities between persons engaged in frequent heroin, frequent cannabis, and less frequent. However, there is also substantial overlap in disrupted neural circuitry across substances (Moreno-Lopez et al., 2012). Further, the heterogenous profiles (i.e. all five substances are used to a certain extent across all profile groups) may reduce differences across groups. It may be that other risk factors not associated with these prominent use profiles would better separate groups on cognitive outcomes (e.g. psychosis).

Though there were no significant findings for cognition, profile groups had reverse rankings for function. That is, while the heroin use group displayed the relative best performance on cognition, their social and occupational functioning was the lowest of the three groups. The findings suggest that it is not likely cognition that explains why the frequent use groups exhibit poorer functioning, but rather may point to other comorbidities or lifestyle factors. Though this does not suggest that cognition does not predict functioning in this group, it is further supported by previous work that suggests that neurocognition does not mediate the relationship between heroin use and functioning (Ersche, Clark, London, Robbins, & Sahakian, 2006; Wang, 2016).

Each profile was associated with demographic and comorbidity factors that could represent risks or consequences that may explain differences in function. While substance use profile groups differed in age, HCV, and depression, these did not appear likely to explain the relatively poorer functioning among the frequent use groups. The Frequent Heroin with Moderate Methamphetamine Use group was significantly younger (poor functioning not due to older age) and HCV was not related to cognition or function. In the current sample, individuals in the frequent heroin using group who had MDE and/or higher rates of depressive symptomology did not appear to function worse than those without signs of depression.

While rates of depressive episodes are higher within frequent use groups, this did not seem to explain their relative difficulties in social and occupational functioning. Similar findings have been found for physical functioning. Past work has suggested that among treatment-seekers with chronic pain, individuals with depressive symptoms were more likely to be taking opioids at higher levels of physical functioning (Goesling et al., 2015). This relationship warrants further study. The relationship between depressive symptoms and substance use profiles could be indicative of affective self-medication (Goesling et al., 2017; Schindler, Thomasius, Peterson, & Sack, 2009) that may mask the effects of depression on functioning. For example, differences in social and occupational functioning may relate to attachment style, such that heroin may be used as an emotional substitute in place of poor coping skills, while cannabis may be used with existing coping strategies involving emotional and social distancing (Schindler, Thomasius, Peterson, & Sack, 2009). However, acute and protracted withdrawal from opioids can include dysphoria and depressive symptoms which can be difficult to differentiate from a major depressive disorder (Center for Substance Abuse Treatment, 2005; Quello, Brady, & Sonne, 2005). As such, differences in depressive symptoms across groups could also reflect withdrawal symptoms that mimic depression (e.g. anhedonia, weight change, fatigue, psychomotor agitation), which may not be indicative of a depressive disorder over and above the results of chronic opioid use.

Together, this suggests that health targets (e.g. social support, lifestyle factors) may be more helpful in predicting and affecting functional change than cognition, particularly for those engaged in frequent use. For example, chronic pain appears to help clarify the multimorbidity associated with polysubstance use, particularly of opioids (Higgins, Smith, & Matthews, 2020; Lake et al., 2019). Further, social networks may explain how patterns emerge and continue based on proximity and type of substance (Knerich et al., 2019), which may have important interactions with the comorbidities and potential success of interventions in this population. Importantly, individuals with comorbid substance use and mood disorders have more severe difficulties and worse clinical outcomes than those with one or the other (Quello, Brady, & Sonne, 2005), making it a primary target for treatment which may be particularly relevant among persons engaged in frequent ongoing use.

Limitations

The present study was limited to a one-year timeframe to maintain power, which may have reduced the expected effect size for cognitive change. However, we were well-powered to detect even a small change. We also chose to investigate average number of days of use per month. While this allowed us to determine clusters based on type and frequency of use with a scale that is consistent across substances, this metric may not capture dosing or binge use. This also resulted in a large moderate use group, which is rather heterogenous and may warrant further investigation. Finally, lack of a healthy control group precludes us from making conclusions about the absolute effects of these substance use profiles on functioning.

Conclusion

Our approach aimed to capture the naturally occurring profiles of substance use in a precariously housed sample to identify whether these profiles were associated with cognitive or functional change over time. The longitudinal mixed design allowed us to evaluate whether ongoing recent substance use was associated with cognitive or functional differences, while accounting for other aspects of substance use including lifetime history and acute use. The present study significantly expands on past work profiling substance use (dichotomous, yes or no) at a single timepoint (Connor, Gullo, White, & Kelly, 2014; Fernandez-Calderon et al., 2011; Harrell, Mancha, Petras, Trenz, & Latimer, 2012; Harrell et al., 2014; Kuramoto, Bohnert, & Latkin, 2011; Monga et al., 2007; Patra, Fischer, Maksimowska, & Rehm, 2009; Trenz et al., 2013). Our results revealed that patterns in type and frequency of substance use can be discerned into meaningful use profiles. These profiles can be used to differentiate people on their relative support needs. As expected, frequent use groups have lower social and occupational functioning than individuals who exhibit infrequent to moderate use. However, there is a discrepancy between cognitive capacity and actual functioning among this group, suggesting that increased substance use can significantly impede function separate from cognitive decline. Support for substance use should aim to target contextual factors that could minimize this discrepancy between capacity and function. For example, it may be more fruitful to focus on pain or social factors than frequency of substance use or cognitive capacity when evaluating support programs aimed at improving function and reducing need for services. In sum, though the polysubstance use in this population may account for cognitive and functional difficulties relative to those who are not homeless and precariously housed, other aspects of health and behaviour may better differentiate the members of this group, which in turn may indicate targets of support that may be overlooked.

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Appendix A. Power Analysis

Effect sizes for substance use on specific and overall cognition are small to moderate (Fernandez-Serrano, Perez-Garcia, & Verdejo-Garcia, 2011; Iverson, 2005; Scott et al., 2007; Verdejo-Garcia, Lopez-Torrecillas, Gimenez, & Perez-Garcia, 2004). Effect sizes for polysubstance use are greater when comparing to control groups but are small to medium when comparing to other user groups (Fernandez-Serrano, Perez-Garcia, Perales, & Verdejo-Garcia, 2010). Effect sizes for cognitive change or group differences in rate of change were expected to be smaller. For example, Sabia and colleagues (2013) found an effect size of $d = 0.24$ for the difference between rates of decline in memory across those consuming over 36 grams of alcohol per day compared to those consuming between 0.1 to 19.9 grams per day. Similarly, effect sizes for one-year practice effects for HVLT delay, FAS, Animals, and TMT A range from $d = -0.03$ to 0.21 (One-year score – baseline score/SD of the difference; Duff et al., 2010).

Cohen (1969) defines $f = 0.10$ as a small effect size, $f = 0.25$ as medium, and $f = 0.40$ as large. Given unequal sample size, power calculations were based on the smallest group (i.e. heroin n x 3). Processing Speed/Executive Control (N = 231), power was approximately 87% to detect a small ($f = 0.125$) interaction effect (rate of change), 92% to detect a small ($f = 0.125$) within-subjects (time) effect, and 89% to detect a medium ($f = 0.275$) between-subjects (profile group) effect. For Verbal Memory (N = 201), power was approximately 82% to detect a small ($f = 0.125$) interaction effect (rate of change), 89% to detect a small ($f = 0.125$) within-subjects (time) effect, and 85% to detect a medium ($f = 0.275$) between-subjects (profile group) effect.

Appendix B. Cognitive Measures

Table B.1. Reliability and Validity for Cognitive Measures

Test	Test-Retest Reliability Estimates (r)	Extra Literature on Validity
CANTAB-RVP	0.71 [1]	[2], [3]
HVLT-R	0.68-0.82 [4], 0.66-0.74 [5], 0.36-0.49 [15]	[6], [15], [18], [21], [22]
TMT A & B	0.79-0.89 [7], 0.36-0.94 [15]	[8], [15], [19], [21], [22]
SDMT	0.84-0.90 [9], 0.89 [10], 0.70 [11], 0.74-0.80 [15]	[12], [15], [21]
Fluency (FAS & Animals)	0.72 [7], 0.70-0.84 [15]	[13], [15], [22]
Stroop	0.84 [7]	[14], [15], [20]
IGT	0.26 [16]	[17]
CANTAB-IED	0.75 [23], [24]	[23], [24]

[1] Goncalves, Pinho, & Simoes (2015)
[2] Fray, Robbins, & Sahakian (1996)
[3] Smith, Need, Cirulli, Chiba-Falek, & Attix (2012)
[4] O'Neill-Pirozzi, Goldstein, Strangman, & Glenn (2011); Total recall: 0.80, Delayed recall: 0.82, Retention: 0.68
[5] Benedict, Schretlen, Groninger, & Brandt (1998); Total recall: 0.74, Delayed recall: 0.66; Recognition: 0.46
[6] Shapiro, Benedict, Schretlen, & Brandt (1999)
[7] Dikmen, Heaton, Grant, & Temkin (1998)
[8] Reitan (1958)
[9] Benedict et al. (2012)
[10] Koh et al. (2011)
[11] Pereira, Costa, & Cerqueira (2015)
[12] Dickinson, Ramsey, & Gold (2007)
[13] Ross et al. (2007)
[14] Golden & Freshwater (1978)
[15] Lezak, Howieson, Bigler, & Tranel (2012)
[16] Buelow & Barnhart (2018)
[17] Barry & Petry (2008)
[18] Stergiopoulos et al. (2019)
[19] Gonzalez, Dieter, Natale, & Tanner (2001)
[20] Foulks, McCown, Duckworth, & Sutker (1990)
[21] Gabrielian et al. (2015)
[22] Barone, Yamamoto, Richardson, Zivanovic, Lin, & Mathas (2019)
[23] Kim, An, Kwon & Shin (2014)
[24] Tyson, Laws, Roberts, & Mortimer (2004)

Appendix C. Missing Data

Table C.1. Missing Data Percentages for Cognition at T1 and T2

	Total N (% Missing) at T1	Total N (% Missing) at T2
HVLT delay	219 (7.2%)	215 (8.9%)
Semantic Fluency (Animals)	218 (7.6%)	217 (8.1%)
Phonemic Fluency (FAS)	219 (7.2%)	212 (10.2%)
Sroop (color-word)	211 (10.6%)	211 (10.6%)
TMT A	230 (2.5%)	225 (4.7%)
TMT B	197 (16.5%)	188 (20.3%)
SDMT (written)	139 (41.1%)	202 (14.4%)
RVP a' std	148 (37.3%)	144 (39.0%)
IED total adjusted errors	182 (22.9%)	158 (33.1%)

Appendix D. Cognitive Results

Table D.1. Raw Scores on Cognitive Testing at Baseline

	N	Minimum	Maximum	Mean	SD
HVLT delay	219	0	12	6.41	3.134
HVLT recognition	218	1	12	9.65	2.388
Semantic Fluency (Animals)	218	2	45	18.56	6.703
Phonemic Fluency (FAS)	219	9	81	35.45	13.793
Stroop (color-word trial)	211	9	86	38.53	11.904
TMT A	230	14	150	39.18	20.863

Table D.2. Raw Scores on Cognitive Testing at Follow-up

	N	Minimum	Maximum	Mean	SD
HVLT delay	215	0	12	6.73	3.171
HVLT recognition	214	0	12	9.52	2.432
Semantic Fluency (Animals)	217	2	39	18.00	5.966
Phonemic Fluency (FAS)	212	6	71	36.30	13.195
Stroop (color-word trial)	211	3	79	37.89	11.192
TMT A	225	15	150	38.64	22.147

Table D.3. Z-score Composites at Baseline

	N	Minimum	Maximum	Mean	SD
Processing Speed/Executive Control	235	-1.91	1.62	-0.0092	0.7151
Verbal Memory	219	-2.63	1.38	-0.0037	0.9102

Table D.4. Z-score Composites at Follow-up

	N	Minimum	Maximum	Mean	SD
Processing Speed/Executive Control	232	-1.75	1.75	-0.0098	0.7059
Verbal Memory	215	-2.52	1.38	0.0253	0.9254

Table D.5. Normative Data

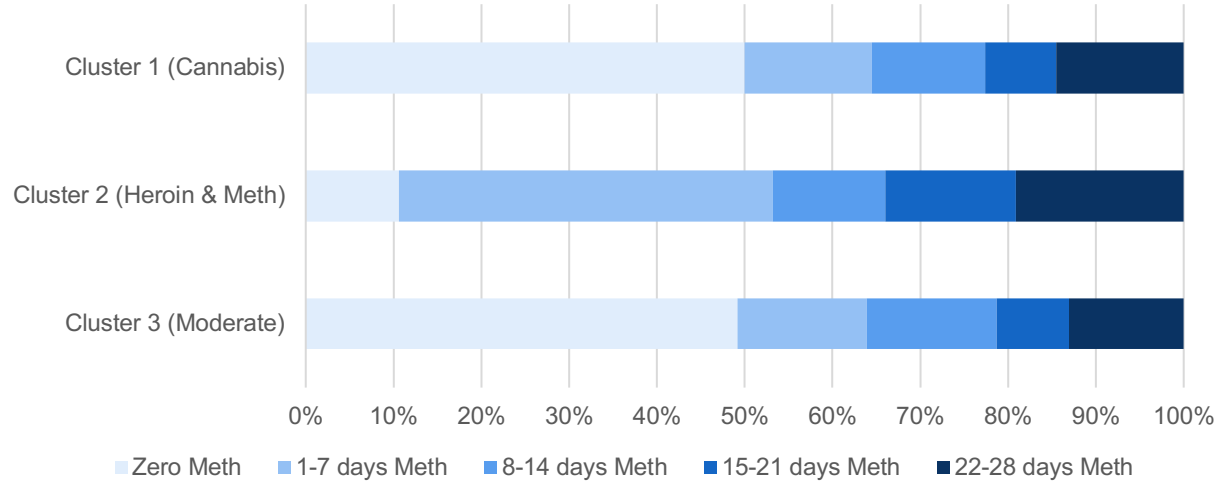
	N	Mean	SD
HVLT delay	127	6.9	3.4
Semantic Fluency (Animals)	127	17.5	5.3
Phonemic Fluency (FAS)	127	38.9	10.8
Stroop (color-word trial)	146	45.4	10.4
TMT A	127	43.6	15.6

Note. Norms based on healthy older adult sample (Mean age: 78.7; Duff et al., 2017), except for the Stroop test. Stroop norms are based on a younger, healthy adult sample (Mean age: 37.5; Morrow, 2013).

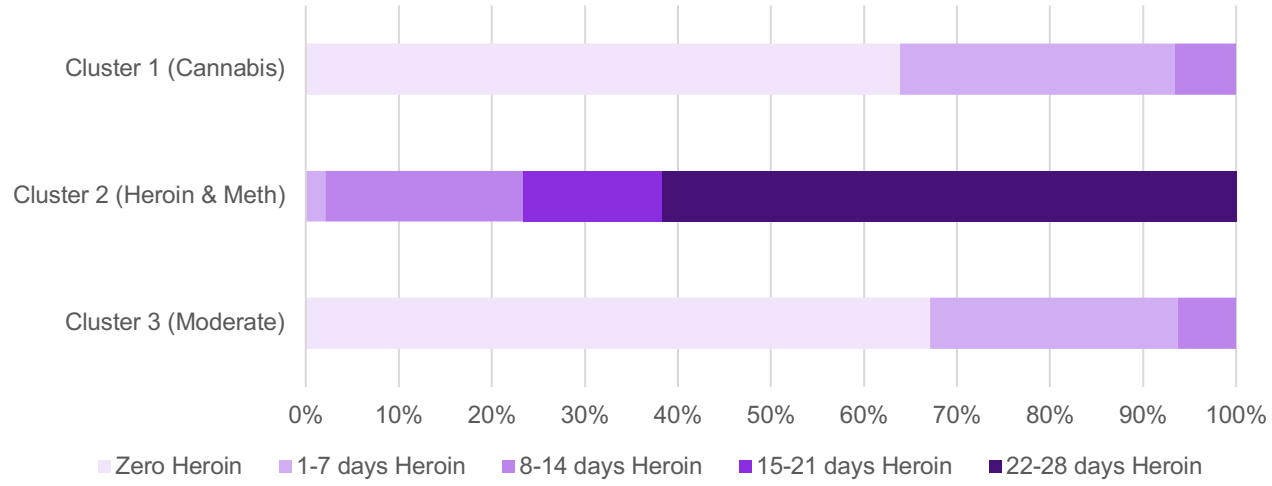
Table D.6. Baseline Sample Average Z-score and Percentile Conversions Based on Healthy Adult Norms

	Z	Percentile
HVLT delay	-0.14	47th
Semantic Fluency (Animals)	0.09	52nd
Phonemic Fluency (FAS)	-0.32	9th
Stroop (color-word trial)	-0.66	8th
TMT A	-0.32	9th

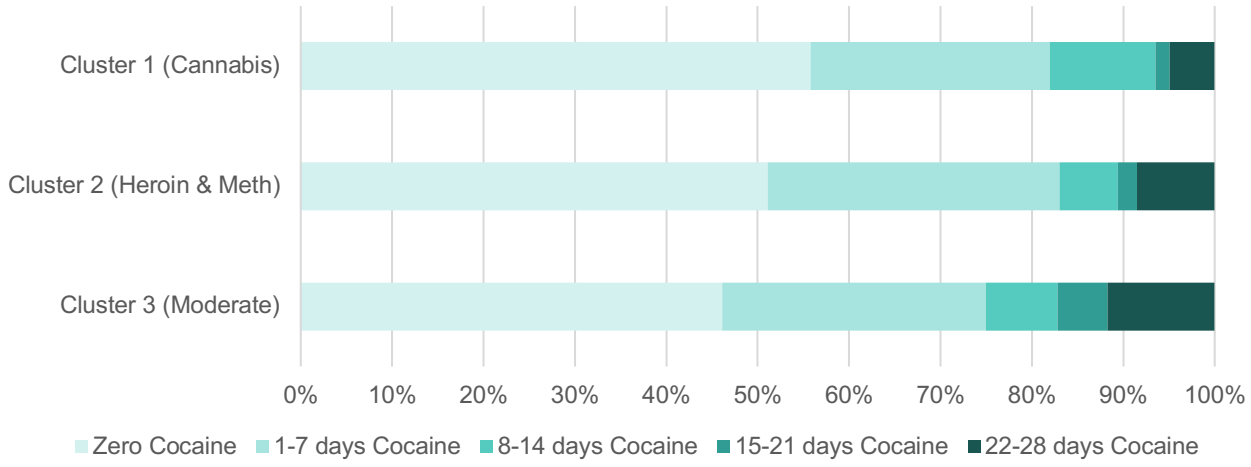
Appendix E. Supplemental Results



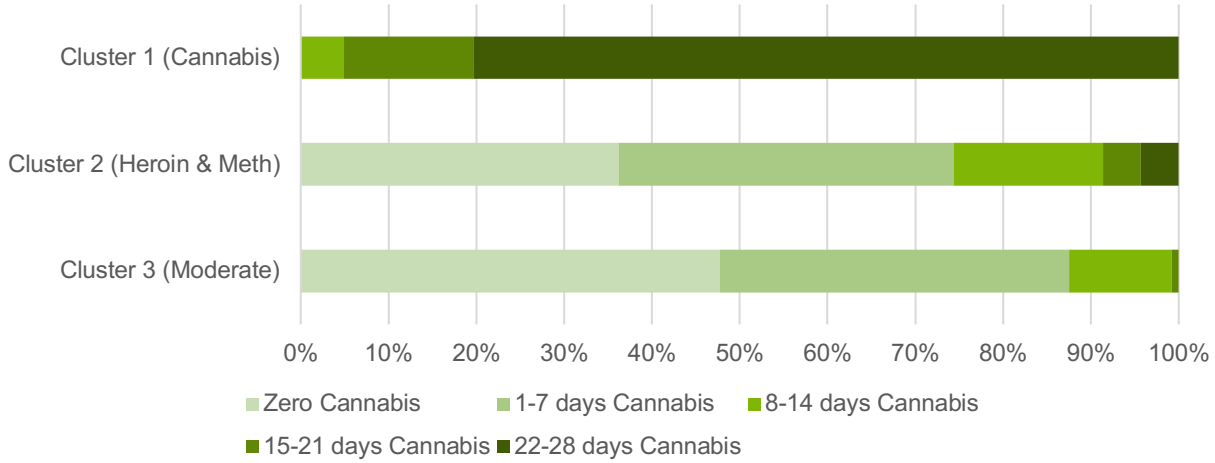
Supplemental Figure 1. Bar Chart of Frequency of Meth Use Across Profiles



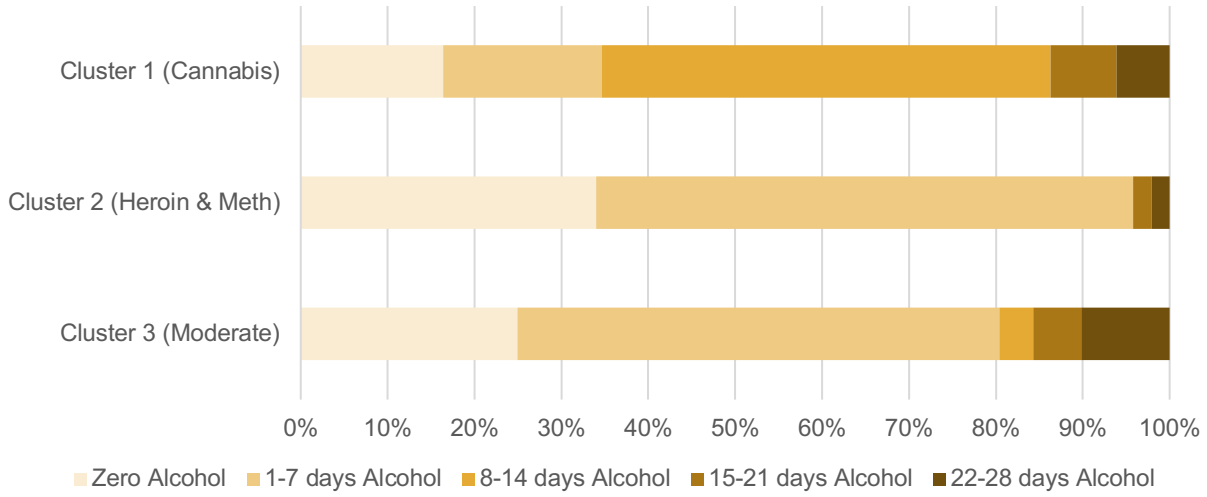
Supplemental Figure 2. Bar Chart of Frequency of Heroin Use Across Profiles



Supplemental Figure 3. Bar Chart of Frequency of Cocaine Use Across Profiles



Supplemental Figure 4. Bar Chart of Frequency of Cannabis Use Across Profiles



Supplemental Figure 5. Bar Chart of Frequency of Alcohol Use Across Profiles

Supplemental Table 1. Lifetime History of Substance Use

Characteristic		Cluster Profile				
		Cannabis (n=61)	Heroin (n=47)	Moderate (n=128)	Test Statistic	Comparison
Lifetime Dependence	Alcohol	65.6%	57.4%	50.8%	$X^2(2)=3.722$	
	Cocaine	27.5%	16.7%	33.3%	$X^2(2)=1.475$	
	Cannabis	45.9%	51.1%	49.2%	$X^2(2)=0.310$	
	Heroin	55.7%	44.7%	61.7%	$X^2(2)=4.103$	
	Meth	44.3%	34.0%	44.5%	$X^2(2)=1.669$	
Age of Onset	Alcohol, Med (IQR) [n=231]	13.00 (3.00)	13.00 (4.00)	14.00 (4.00)	H=4.756	
	Cannabis, M (SD)** [n=230]	13.39 (3.91)	12.91 (2.37)	14.89 (4.52)	$F_{2,233}=5.308$	M>H, M>C
	Cocaine, Med (IQR)* [n=228]	17.50 (9.00)	18.00 (5.00)	19.00 (8.00)	H=7.030	M>H
	Opioid, Med (IQR) [n=211]	21.50 (11.00)	20.00 (10.00)	21.00 (12.00)	H=1.510	
	Amphetamine, Med (IQR) [n=192]	23.00 (16.00)	20.00 (15.00)	20.50 (17.00)	H=1.681	

Note. N = 236, unless otherwise specified. † Dependence diagnoses based on BECED at study entry. Significance adjusted for multiple comparisons (i.e. Tukey's HSD and Bonferroni).

*Significant to $p < 0.05$. **Significant to $p < 0.01$.

Supplemental Table 2. Acute Substance Use

Characteristic		Cluster Profile				
		Cannabis (n=61)	Heroin (n=47)	Moderate (n=128)	Test Statistic	Comparison
Acute Use at Baseline	Alcohol (24 hours)	21.3%	12.8%	19.5%	$X^2(2)=1.423$	
	Cannabis (48 hours)** [n=235]	54.1%	14.9%	11.8%	$X^2(2)=43.479$	C>H, C>M
	Cannabis (UDS)** [n=161]	90.5%	34.5%	24.4%	$X^2(2)=51.973$	C>H, C>M
	Cocaine (48 hours)* [n=235]	9.8%	12.8%	26.8%	$X^2(2)=9.237$	M>C
	Cocaine (UDS) [n=161]	40.5%	37.9%	41.1%	$X^2(2)=0.092$	
	Meth (48 hours)** [n=235]	31.1%	34.0%	15.0%	$X^2(2)=10.164$	H>M, C>M
	Meth (UDS)** [n=161]	40.5%	79.3%	35.6%	$X^2(2)=17.399$	H>M, H>M
	Opioid (48 hours)** [n=235]	11.5%	74.5%	14.2%	$X^2(2)=74.155$	H>M, H>C
	Opioid (UDS)** [n=160]	19.5%	82.8%	27.8%	$X^2(2)=35.150$	H>M, C>M
Acute Use at Follow-Up	Alcohol (24 hours)*	26.2%	4.3%	21.1%	$X^2(2)=9.050$	C>H, M>H
	Cannabis (48 hours)** [n=232]	67.8%	8.7%	11.8%	$X^2(2)=75.058$	C>H, C>M
	Cannabis (UDS)** [n=157]	80.5%	35.5%	28.2%	$X^2(2)=31.721$	C>H, C>M
	Cocaine (48 hours) [n=232]	20.3%	8.7%	22.0%	$X^2(2)=4.014$	
	Cocaine (UDS) [n=156]	45.0%	32.3%	48.2%	$X^2(2)=2.364$	
	Meth (48 hours)** [n=232]	32.2%	41.3%	15.7%	$X^2(2)=13.952$	H>M, C>M
	Meth (UDS)** [n=158]	48.8%	78.1%	41.2%	$X^2(2)=12.773$	H>M, H>C
	Opioid (48 hours)** [n=232]	10.2%	73.9%	10.2%	$X^2(2)=84.895$	H>M, H>C
	Opioid (UDS)** [n=158]	19.5%	82.8%	27.8%	$X^2(2)=35.150$	H>M, C>M

Note. N = 236, unless otherwise specified. Significance adjusted for multiple comparisons (Bonferroni method). Patterns of acute use were similar across time points, except for alcohol within the heroin use group. Of those whose urine tested positive for opioids at baseline, 70.5% were also positive at follow-up. Similarly, rates for those who tested positive for cannabis (Δ9-THC), cocaine, and methamphetamine were 78.6%, 75.5%, and 87.0% at follow-up, respectively.
*Significant to $p < 0.05$. **Significant to $p < 0.01$.

Supplemental Table 3. UDS for Opioids

Characteristic		Cluster Profile		
		Cannabis (n=61)	Heroin (n=47)	Moderate (n=128)
% of Participants †	Fentanyl [n=47]	33.3%	100.0%	29.6%
	Methadone [n = 153]	26.3%	43.3%	40.0%
	Morphine [n = 37]	22.2%	100.0%	36.4%
	Oxycodone [n = 49]	8.3%	12.5%	0.0%
	Hydromorphone [n = 34]	33.3%	100.0%	42.1%
% Positive (UDS)	Fentanyl, Med (IQR)** [n=47]	0.00 (0.24)	1.00 (0.16)	0.00 (0.25)
	Methadone, Med (IQR) [n=153]	0.00 (0.21)	0.00 (0.85)	0.00 (1.00)
	Morphine, Med (IQR)** [n=37]	0.00 (0.13)	0.63 (0.56)	0.00 (0.42)
	Oxycodone, Med (IQR) [n=49]	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)
	Hydromorphone, Med (IQR)** [n=34]	0.00 (0.23)	1.00 (0.06)	0.00 (0.67)

Note. N = 236, unless otherwise specified.

† Percent of participants with at least one positive UDS over the year.

Supplemental Table 4. Post Hoc Multiple Comparisons for Profile Group Differences in Functioning

I	J	Mean Difference (I – J)	Sig
Cannabis	Heroin	1.354	1.000
	Moderate	-2.993	0.051
Heroin	Cannabis	-1.354	1.000
	Moderate**	-4.347	0.005
Moderate	Cannabis	2.993	0.051
	Heroin**	4.347	0.005

Note. N = 221. Significance adjusted for multiple comparisons using Tukey's HSD procedure. **Significant to $p < 0.01$.