



Factors affecting severity of positive and negative symptoms of psychosis in a polysubstance using population with psychostimulant dependence



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ABSTRACT

Approximately half of psychostimulant users experience psychotic symptoms, which include both positive and negative symptoms. Prior reports have exclusively used positive symptoms to characterize psychostimulant associated psychosis. Symptoms vary dramatically in severity, though most investigations categorize psychosis as a dichotomous occurrence. To explore the association between different substances of abuse and the severity of psychotic symptoms, we investigated 171 individuals meeting DSM-IV-TR criteria for psychostimulant (cocaine or methamphetamine) dependence in an observational cross-sectional study. Participants were predominantly male (72.5%), recruited from a socially disadvantaged neighborhood in Vancouver, Canada, with a mean age of 45.5 (± 8.8) years. Of the total sample, 85% were dependent on cocaine, and 28.1% were dependent on methamphetamine. Participants had a median total PANSS score of 63, ranging from 37 to 111. Demographic information, current substance use and early substance exposure were used to predict positive and negative psychotic symptom severity in linear regression models. Increased severity of positive psychotic symptoms was significantly related to greater methamphetamine and marijuana use in the past 28 days, and methadone-abstinence. Negative symptom severity was related to increased opioid use in the past 28 days. There was no overlap between predictors of positive and negative symptom severity.

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1. Introduction

Psychostimulants, including amphetamines and cocaine, are the second most commonly used illicit substances worldwide, with an estimated 28–75 million users (World Drug Report, 2014). In urban communities, the rates and heterogeneity of psychostimulant use become even more prevalent (Fischer et al., 2006; Kuramoto et al., 2011). At low doses these drugs generate feelings of increased energy and mood, while frequent exposure and higher doses can lead to a host of adverse effects, including physical (e.g. strokes, seizures, arrhythmias) and psychiatric complications (e.g. dependency, depression, anxiety, psychosis) (Barr et al., 2006).

Approximately 50–75% of cocaine users (Brady, 1991; Mooney

et al., 2006; Satel and Edell, 1991; Smith et al., 2009; Vergara-Moragues et al., 2014; Vorspan et al., 2012) and 50–60% of methamphetamine users (Grant et al., 2012; Hall et al., 1996; McKetin et al., 2006; Smith et al., 2009) experience psychotic symptoms during consumption, including paranoia, delusions, and vivid sensory hallucinations (Alam Mehrjerdi et al., 2013; Mahoney et al., 2008). Though high frequencies of psychotic symptoms have been reported in both methamphetamine and cocaine users, direct comparison has shown that methamphetamine users more commonly exhibit psychotic symptoms than cocaine users (Mahoney et al., 2008).

Due to their high prevalence and severity, positive symptoms have been the hallmark of characterizing psychostimulant-associated psychosis (Panenka et al., 2013; Zorick et al., 2008). These positive symptoms are frequently indistinguishable from the positive symptoms of schizophrenia spectrum disorders (Shaner et al., 1998; Zorick et al., 2008). While there is some evidence that

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negative symptoms are also present in psychostimulant-associated psychosis (Srisurapanont et al., 2011), others have theorized that the absence of negative symptoms in psychostimulant-associated psychosis may be a key differentiating factor from schizophrenia spectrum disorders (Zorick et al., 2008). The prevalence and severity of negative symptoms in psychostimulant-associated psychosis is thus an ongoing subject of debate (Panenka et al., 2013; Srisurapanont et al., 2011; Zorick et al., 2008).

The presentation of psychotic symptoms ranges in severity from subclinical psychotic experiences, to psychotic symptoms with varying functional impact, to clinically significant psychotic disorders (Binbay et al., 2012; van Os, 2014). Even though psychostimulant use causes psychosis across a spectrum of severity, most studies report psychosis as a dichotomous categorical occurrence. Only a small number of studies have investigated the severity of current positive symptoms, noting that chronic use (greater than 5 years), weekly use pattern, and injection administration are significant predictors of greater symptom severity (Lichlyter et al., 2011; Vorspan et al., 2012). However, Vorspan et al. was limited to studying only cocaine users, while Lichlyter et al. performed their study in a 30-day stimulant-abstinent sample. Thus, the effect of recent psychostimulant use on psychotic symptom severity is lacking, and has never been evaluated in the context of negative symptoms. When investigated as a categorical outcome (i.e. present or not), identified risk factors for psychostimulant associated psychosis have included earlier age of first use (Chen et al., 2003; Farrell et al., 2002; Kalayasiri et al., 2006a; Roncero et al., 2014), severity of dependence (Farrell et al., 2002; Kalayasiri et al., 2006a; Vergara-Moragues et al., 2014), marijuana dependence (Farrell et al., 2002; Kalayasiri et al., 2010; Roncero et al., 2013, 2014), route of administration (Hall et al., 1996), and recent frequency of use (McKetin et al., 2013). However, categorically defining psychostimulant-induced psychosis may not capture important information when psychosis occurs on a continuum of severity (Binbay et al., 2012; van Os, 2014). Simplifying psychosis to a binary outcome requires the establishment of a threshold, which varies among studies. Some studies define psychostimulant associated psychosis as any lifetime occurrence of a symptom, which may be too broad of an inclusion parameter (Kalayasiri et al., 2006a; Roncero et al., 2014). Other studies require a diagnosis according to standardized criteria (Farrell et al., 2002; Willi et al., 2016), thus excluding moderately symptomatic states, which may overlook risk factors pertinent to moving along the continuum of psychosis (Yung et al., 2003). By utilizing different thresholds for definitions of psychosis, repeatability can be problematic and impede study-to-study comparisons.

The aim of the current study was to identify risk factors that contribute to the spectrum of psychotic severity presenting concurrently with psychostimulant abuse, in both positive and negative dimensions. We hypothesized that variables regarding recent frequency of use would be the strongest predictors of current symptom severity, with greater use associated with greater symptom severity. Here, we describe the results of regression models to help explain the variance of psychosis symptom severity in a psychostimulant dependent population.

2. Methods

2.1. Sample

Participants were selected from the ongoing Hotel Study, an observational longitudinal cohort study of multimorbidity in the Downtown Eastside (DTES) of Vancouver, British Columbia (Vila-Rodriguez et al., 2013). In this cohort of 370 individuals, all cases of past or present psychosis not related to substance abuse were excluded, including schizophrenia, schizoaffective disorder, bipolar with psychosis, major depressive disorder with psychosis, or psychosis not otherwise

specified according to DSM-IV-TR criteria. From the remaining 243 participants, inclusion criteria were current psychostimulant dependence at study entry (DSM-IV-TR criteria) and an available Positive and Negative Symptom Syndrome (PANSS) baseline assessment, resulting in the retention of 179 participants. In accordance to Tri-Council policy, the study was approved by the University of British Columbia Clinical Research Ethics Board. All participants provided written informed consent.

2.2. Measures

Demographic information including age, gender, and education were collected. Psychiatric health and substance use disorders were assessed according to DSM-IV-TR diagnostic criteria through consensus with the Best Estimate Clinical Evaluation and Diagnosis (BECED; Endicott, 1988) by an experienced psychiatrist (WGH, OL, or FVR).

Frequency of drug use was retrospectively collected for the 28 days prior to psychiatric assessment with the Time Line Follow Back method (TLFB; Sobell et al., 1986). Drug use frequency was divided by 7 to obtain weeks of use per month. Methadone status was recorded as either positive or abstinent. A urine drug screen was collected at time of psychiatric assessment to validate self-reported data. In instances where no psychostimulant use was reported in the past 28 days, and a urine drug screen was positive, data were omitted from analysis (8 cases, final $n = 171$). Years of regular substance usage and age of first usage were provided via self-report.

Severity of psychotic symptomatology was assessed using the PANSS (Kay et al., 1987). For the positive dimension, PANSS items P1 (delusions), P3 (hallucinations), P5 (grandiosity), P6 (suspiciousness), G9 (unusual thought content), and G12 (insight) were summed, as previously described using a 5-dimensional factor (potential range: 6–42) (Emsley et al., 2003). For the negative dimension, PANSS items N1 (blunted affect), N2 (emotional withdrawal), N3 (poor rapport), N4 (social withdrawal), N6 (lack of spontaneity), G7 (motor retardation), G13 (disturbance of volition), and G16 (social avoidance) were summed, as previously described (potential range: 7–49) (Emsley et al., 2003).

2.3. Analysis

Data were analyzed using SPSS software version 22 (SPSS Inc., IBM Corp., Armonk, USA). Descriptive statistics were calculated for all variables.

To pre-screen variables of interest before entry into a statistical model, bivariate analyses between variables of interest and the sum of positive symptoms (P1, P3, P5, P6, G9, and G12) or negative symptoms (N1, N2, N3, N4, N6, G7, G13, G16) were performed using a Pearson Correlation.

Pre-screened variables with at least a weak association with the symptom severity outcome ($p < 0.20$) were entered into a multiple linear regression model. Model optimization was performed by utilizing a backward elimination model selection approach, where the least significant variable (if $p > 0.10$) was dropped from the model. This process was repeated until all variables in the model met criteria ($p < 0.10$). Potential interaction effects were explored between the independent variables, and tested for significance at $p < 0.05$. Collinearity between independent variables was tested for with the variance inflation factor (VIF).

To investigate possible associations with specific psychotic symptoms, Pearson correlations were performed in a secondary exploratory analysis between significant independent variables from the regression models and the individual PANSS items. Positive symptom PANSS items P1, P3, P5, P6, G9, and G12 were checked for correlations with independent variables of the positive symptom regression, while negative symptom PANSS items N1, N2, N3, N4, N6, G7, G13, G16 were checked for correlations with independent variables of the negative symptom regression.

Potential effects of cocaine use frequency on psychotic symptoms were further investigated in two ways: first, by analyzing individuals with cocaine dependency and concurrent cocaine and methamphetamine dependency (n analyzed = 144) and second, by excluding all participants dependent on methamphetamine, leaving only cocaine dependent participants ($n = 122$). Differences in symptom severity based on type of cocaine (powder or crack) were investigated with a Student's t -test.

The other three dimensions of the 5 factor PANSS model were similarly assessed with optimization of a multiple linear regression model in supplementary analysis, including: Disorganization (sum of P2, N5, N7, G5, G10, G11, and G15), Excitement (sum of P4, P7, G8, and G14), and Anxiety/Depression (G1, G2, G3, G4, and G6) (Emsley et al., 2003).

3. Results

3.1. Descriptive

A total of 171 participants were investigated in this analysis. Table 1 describes the socio-demographic characteristics of the

Table 1
Demographics.

	Total (n = 171)	Positive symptoms ^a		Negative symptoms ^b	
		Pearson's r	p-value	Pearson's r	p-value
Age in years (SD)	45.5 (8.8)	–0.070	0.360	–0.103	0.178
Female (%)	27.5%	–0.108	0.161	0.122	0.111
Education in years (SD)	10.1 (2.1)	–0.071	0.362	–0.123	0.112
Methadone status (%)	50.90%	–0.210**	0.006	0.091	0.236
Marijuana frequency (Days/Last Month)	7.6 (11.4)	0.227**	0.003	–0.030	0.698
Meth frequency (Days/Last Month)	4.0 (8.1)	0.193*	0.011	0.075	0.330
Cocaine frequency (Days/Last Month)	14.9 (11.6)	–0.066	0.394	0.136	0.077
Opioid frequency (Days/Last Month)	8.6 (11.3)	0.024	0.755	0.163*	0.033
Alcohol frequency (Days/Last Month)	2.6 (6.2)	0.056	0.464	–0.159*	0.038
Psychostimulant IV in last month (%)	44.40%	0.101	0.188	–0.010	0.896
Years psychostimulants (SD)	14.7 (10.0)	0.050	0.519	–0.042	0.591
Years cocaine (SD)	13.8 (10.0)	0.034	0.663	–0.045	0.562
Years amphetamines (SD)	3.5 (6.6)	0.013	0.877	0.024	0.771
Years alcohol (SD)	12.7 (11.3)	0.090	0.247	–0.156*	0.044
Years marijuana (SD)	14.2 (12.5)	0.104	0.182	0.024	0.761
Years hallucinogens (SD)	2.8 (6.6)	0.077	0.370	–0.018	0.831
Years injecting (SD)	15.4 (12.3)	–0.076	0.373	–0.114	0.180
Age first use marijuana (SD)	18.5 (5.4)	–0.054	0.481	–0.095	0.217
Age first use cocaine (SD)	21.2 (9.0)	0.017	0.833	–0.002	0.978
Age first use psychostimulants (SD)	21.6 (8.9)	0.009	0.911	0.002	0.977
Age first use hallucinogens (SD)	16.7 (3.9)	0.061	0.459	–0.076	0.355
Age first use opioids (SD)	23.7 (9.4)	–0.044	0.587	0.044	0.580
Age first injection (SD)	22.8 (9.0)	–0.023	0.785	0.095	0.258

^a Positive symptoms = sum of PANSS items P1, P3, P5, P6, G9, and G12.

^b Negative symptoms = sum of PANSS items N1, N2, N3, N4, N6, G7, G13, G16.

* $P < 0.05$.

** $P < 0.01$.

sample. Typically, participants were middle-aged males with an incomplete high school education. Concurrent mood disorders were present in a small subset of the sample – 11.6% had a DSM-IV TR diagnosis of major depressive disorder, while 3.5% of the sample had a diagnosis of bipolar disorder. Of the total sample, 92.7% of the participants were currently unemployed, 59.6% had at least one previous incarceration, and 47.2% had received medication or treatment for mental illness at some point in their lives.

All participants were clinically dependent on a psychostimulant – cocaine (85%) or methamphetamine (28.1%). In the month prior to assessment, other drug use in the sample included marijuana (42.7%), opioid (54.4%), alcohol (43.35%), and methadone (52.3%). In the 28 days prior to psychiatric assessment, cocaine was the most frequently used drug in the sample, with an average (SD) of 14.9 (11.6) days of use. There was an average of 8.5 (11.3) days of opioid use, 7.6 (11.4) days of marijuana use, and 4.0 (8.1) days of methamphetamine use.

The mean age of first psychostimulant use (SD) was 21.6 (8.9), while the average duration of regular psychostimulant use was 14.7 years (10.0). The mean age of first marijuana use was 13.7 (3.2), with an average duration of regular use of 14.2 years (12.5). See Table 1 for all substance use data.

The mean positive factor PANSS score was 13.0 (4.0) with an observed range of 6–28. The mean negative factor PANSS score was 16.3 (5.6) with an observed range of 8–35. The mean total PANSS score was 64.1 (13.8) with an observed range of 37–111.

3.2. Symptom severity bivariate analysis

Increases in positive symptom severity were significantly associated ($p < 0.05$) with an increased frequency of methamphetamine and marijuana use. Methadone-positive status was associated with decreases in positive symptom severity. Increases in positive symptom severity showed a weak association ($p < 0.20$) with male gender, injection route of psychostimulant and years of

regular marijuana use. No significant associations were present with cocaine frequency (Pearson's $r = -0.066$, $p = 0.394$).

Increases in negative symptom severity were significantly associated ($p < 0.05$) with an increased frequency of opioid use and alcohol use in the past 28 days, and years of regular alcohol use. Increases in negative symptom severity showed a weak association ($p < 0.20$) with younger age, female gender, less education, an increased frequency of cocaine use, and less years of injecting psychostimulants.

Concurrent mood disorders (major depressive disorder or bipolar disorder), were not associated with PANSS positive or negative subscale severity, all $p > 0.40$.

See Table 1 for all associations tested.

3.3. Positive symptom severity multivariable analysis

In a multiple linear regression model, positive symptom severity was the dependent variable with the pre-screened variables (Section 3.2) entered as independent variables including weeks of methamphetamine use in the last 28 days, weeks of marijuana use in the last 28 days, methadone status, gender, injection of psychostimulants in the last 28 days, and years of marijuana use. Methamphetamine frequency, marijuana frequency, and methadone status all explained a significant amount of the variance in the regression model ($p < 0.05$).

For each week increase of methamphetamine use in the past 28 days, the Positive PANSS severity increased by 0.52 points. For each week increase of marijuana use in the past 28 days, Positive PANSS severity increased by 0.38 points. Methadone positive status resulted in a decrease of 1.33 Positive points, relative to methadone-abstinent participants.

The final model was found to explain 10.0% of the variation in positive symptoms as measured with the PANSS ($R = 0.317$, $R^2 = 0.100$ ANOVA $F(5, df) = 6.219$, $p < 0.001$). Individual regression coefficients can be found in Table 2. No significant interaction

Table 2
Multivariate analysis for positive and negative symptom severity models.

		Multivariable		
		β -Unstandardized (Std error)	β -Standardized	p-value
Positive symptom regression	MA frequency (weeks/previous month)	0.518 (0.259)	0.152	0.045
	MJ frequency (weeks/previous month)	0.378 (0.189)	0.157	0.043
	Methadone status (0=abstinent, 1=positive)	−1.331 (0.594)	−0.169	0.026
Negative symptom regression	Opioid frequency (weeks/previous month)	0.910 (0.287)	0.267	0.002
	Regular years injecting psychostimulants	−0.073 (0.038)	−0.159	0.059

Positive Regression Model $R^2=0.115$, ANOVA $F(3 \text{ df})=6.967$; Negative Regression Model $R^2=0.082$, ANOVA $F(2 \text{ df})=6.014$. MA=methamphetamine. MJ=marijuana.

effects were present between any of the predictor variables (all $p > 0.10$), and all VIF < 1.2 .

3.4. Negative symptom severity multivariate analysis

In a multiple regression model, negative symptom severity was treated as the dependent variable with the pre-screened variables opioid frequency of use in the past 28 days, alcohol frequency of use in the past 28 days, total years of regular alcohol use, age, gender, education, frequency of cocaine used in the past 28 days, and years of injecting psychostimulants were entered as independent variables. Frequency of opioid use in the past 28 days was the only independent variable that explained a significant amount of the variance in the regression model ($p=0.002$).

For each week of opioid use in the past 28 days, negative symptom severity increased by 0.91 points. The model explained 8.2% of the variation in negative symptoms as measured with the PANSS ($R=0.286$, $R^2=0.082$, ANOVA $F(3 \text{ df})=6.014$, $p=0.003$). Individual regression coefficients can be found in Table 2. No significant interaction effects were present between any of the predictor variables (all $p > 0.08$).

3.5. Supplementary analysis

3.5.1. Specific symptom supplementary analysis

In exploratory analysis, increased delusions (P1), grandiose thoughts (P5), and unusual thought content (G9) were all significantly associated with both increased methamphetamine frequency and marijuana frequency, while methadone-positive status was associated with diminished delusions (P1). Increased opioid frequency was specifically associated with increased negative symptoms of emotional withdrawal, social withdrawal, and motor retardation. All associations can be found in Table 3. As a secondary analysis exploring specific components of results from the primary analysis, a Bonferroni correction was not applied to the multiple correlations tested.

3.5.2. Cocaine frequency supplementary analysis

Cocaine frequency was not correlated with current positive symptom severity when all methamphetamine users were excluded ($n=112$; Pearson's $r=-0.025$, $p=0.793$), or when

analyzing cocaine and concurrent cocaine/methamphetamine users ($n=145$; Pearson's $r=-0.005$, $p=0.954$). When cocaine powder users were compared to cocaine crack users, no statistical difference in symptom severity was present in either cocaine subgroup ($n=122$: $t=0.602$, $p=0.549$; $n=144$: $t=1.308$, $p=0.193$).

3.5.2.1. Excitement symptom severity supplementary analysis. The PANSS 5-factor dimension of Excitement (P4, P7, G8, G14) was generally associated ($p < 0.20$) with an increased frequency of cocaine use in the past 28 days ($n=168$; Pearson's $r=0.166$, $p=0.032$), younger age ($n=171$; Pearson's $r=-0.176$, $p=0.022$), not injecting psychostimulants ($n=169$; Pearson's $r=-0.138$, $p=0.075$), younger age of first cocaine use ($n=161$; Pearson's $r=-0.152$, $p=0.055$), and years of regular psychostimulant use ($n=167$; Pearson's $r=0.139$, $p=0.073$). In the multiple regression model, frequency of cocaine use in the past 28 days ($\beta(\text{st error})=0.38(0.15)$, $p=0.014$) and age ($\beta(\text{st error})=-0.072(0.28)$, $p=0.011$) explained a significant amount of the variance of the final model. An increased frequency of cocaine use was specifically associated with an increase of the excitement symptoms of uncooperativeness (G8 Pearson's $r=0.289$, $p=0.001$) and hostility (P7 Pearson's $r=0.151$, $p=0.049$).

3.5.2.2. Anxiety/Depression symptom severity supplementary analysis. The PANSS 5-factor dimension of Anxiety/Depression (G1, G2, G3, G4, G6) was generally associated ($p < 0.20$) with female gender ($n=168$; Pearson's $r=0.147$, $p=0.057$), a decreased frequency of cocaine use in the past 28 days ($n=167$; Pearson's $r=-0.106$, $p=0.172$), and a decreased frequency of alcohol use in the past 28 days ($n=168$; Pearson's $r=-0.208$, $p=0.007$). In the final multiple regression model, frequency of alcohol use in the past 28 days ($\beta(\text{st error})=-0.89(0.33)$, $p=0.007$) explained a significant amount of the variance in the model. An increased frequency of alcohol use was specifically associated with a decrease of the depression/anxiety symptoms of somatic concern (G1 Pearson's $r=-0.159$, $p=0.037$), anxiety (G2 Pearson's $r=-0.162$, $p=0.034$), and tension (G4 Pearson's $r=-0.165$, $p=0.032$).

3.5.2.3. Disorganization symptom severity supplementary analysis. The PANSS 5-factor dimension of Disorganization (P2, N5, N7, G5, G10, G11, G15) was generally associated ($p < 0.20$) with education

Table 3
Associations between significant predictor variables and Specific PANSS symptoms.

	Symptom	r	p	Symptom	r	p	Symptom	r	p
Methamphetamine frequency	Delusions (P1)	0.18	0.019	Grandiose Thoughts (P5)	0.155	0.043	Unusual Thought Content (G9)	0.271	0.001
Marijuana frequency	Delusions (P1)	0.276	0.001	Grandiose Thoughts (P5)	0.177	0.021	Unusual Thought Content (G9)	0.18	0.019
Methadone status	Delusions (P1)	−0.228	0.003						
Opioid frequency	Emotional Withdrawal (N2)	0.179	0.019	Social Withdrawal (N4)	0.175	0.022	Motor Retardation (G7)	0.195	0.011

Frequency variables refer to the frequency of drug use in the past 28 days. R refers to the Pearson correlation coefficient, p refers to the statistical significance of this coefficient.

completed ($n = 167$; Pearson's $r = -0.133$, $p = 0.088$), and the age of first marijuana use ($n = 169$; Pearson's $r = 0.103$, $p = 0.183$). In the multiple regression model, no variables explained a significant amount of the variance in the regression model.

4. Discussion

In a sample of polysubstance using individuals with psychostimulant dependence, we report that the severity of current positive psychotic symptoms – primarily the severity of delusions – is significantly related to methadone-abstinent status and an increased frequency of methamphetamine and marijuana use in the past 28 days. Current negative psychotic symptoms were not associated with any of the predictors of positive symptom severity, though they were significantly related to the frequency of opioid use in the past 28 days. Cocaine frequency of use was unrelated to symptom severity.

The largest contributor to current positive symptom severity was the frequency of methamphetamine use in the past 28 days. The relationship between methamphetamine and psychosis severity is supported by a literature describing frequency of methamphetamine use as a major predictor of categorically defined psychosis (Farrell et al., 2002; Hall et al., 1996). McKetin et al. (2013) followed methamphetamine users longitudinally to demonstrate a strong dose-dependent relationship between frequency of methamphetamine use and the presence of a clinically significant psychotic symptom. Increased lifetime duration of psychostimulant use (Lecomte et al., 2013; Lichlyter et al., 2011) and earlier age of first psychostimulant use (Farrell et al., 2002; Lichlyter et al., 2011; Power et al., 2014; Roncero et al., 2014; Vorspan et al., 2012) have also been associated with the presence of psychotic symptoms. Although these parameters of psychostimulant use may be predictive of categorically defined psychosis, this relationship does not seem to extend to the severity of symptoms currently experienced. This notion is supported by Salo et al. (2008), who reported no association between years of psychostimulant use or age of first use in differentiating methamphetamine abusers with frequent versus infrequent psychotic experiences.

The frequency of marijuana use in the past 28 days was also a significant contributor to the variance seen in current positive symptom severity. Thus increased use of marijuana in psychostimulant dependent individuals was associated with more severe psychosis. The hypothetical link between marijuana and the development of organic psychoses has long been recognized, with leading theories suggesting that marijuana can precipitate psychosis in otherwise vulnerable individuals (Caspi et al., 2005; Degenhardt et al., 2003; Henquet et al., 2005; Murray et al., 2007). Studies exclusively investigating cocaine users found that early marijuana exposure was a risk factor for cocaine-dependent individuals to develop cocaine-induced psychosis (Kalayasiri et al., 2010). Additionally, meta-analysis has shown that continued marijuana use after psychosis onset predicts higher relapse rates and more severe positive symptoms than individuals who discontinue marijuana use (Schoeler et al., 2016). However, a common alternative explanation for the marijuana/psychosis correlation is one of “self-medication”, whereby persons experiencing prodromal symptoms use marijuana to self-medicate their distress (Hambrecht et al., 2000; Henquet et al., 2005). This hypothesis supports an indirect association between marijuana and psychosis. Bianconi et al. (2016) have suggested that the association between marijuana and psychosis may be due to a hypersensitivity in individuals with past psychotic experiences, leading to both greater enjoyment and exacerbated psychotic symptoms. It is important to note that the current study exclusively investigated

psychostimulant dependent individuals: thus, the role of marijuana in psychotic symptom severity may be different in individuals that have not experienced heavy stimulant exposure.

A relationship between positive symptoms and methamphetamine or marijuana frequency of use is consistent with existing literature on risk factors for psychostimulant associated psychosis (Farrell et al., 2002; Kalayasiri et al., 2010; Lichlyter et al., 2011; McKetin et al., 2006). However, we unexpectedly found no association between frequency of cocaine use and positive or negative symptom severity. This may reflect the relatively more severe physiological effects of methamphetamine when compared to cocaine (Cook, 1991; Mahoney et al., 2008). Mahoney et al. (2008) showed that in a direct comparison of methamphetamine dependent to cocaine dependent individuals, psychotic symptoms were observed more frequently in the methamphetamine group, in both abstinent and intoxicated states. Additionally, methamphetamine has a significantly longer half-life than cocaine, possibly increasing the likelihood that we were capturing acute psychotic symptoms in the methamphetamine group. Furthermore, the longer half-life of methamphetamine may result in greater sleep deprivation which could contribute to psychosis (Ciccarone et al., 2011; Mahoney et al., 2014; Ujike and Sato, 2004). Thus, the psychotic-inducing effects of methamphetamine may be masking the effects of cocaine in this population (Mahoney et al., 2008). However, in the present study, when methamphetamine users were excluded in supplementary analysis, the frequency of cocaine use was still not related to positive symptom severity. In supplementary analysis of other dimensions of the 5 factor PANSS, cocaine frequency of use was significantly associated with the factor of excited symptom severity, indicating that the PANSS was sensitive to our index of cocaine use. The absence of a relationship between the severity of positive symptoms and cocaine use was not expected; while the explanation for this requires further study, we suggest that one factor involved may be related to recorded patterns of cocaine ingestion. The Time Line Follow Back questionnaire is not able to determine if subjects consumed cocaine as part of a “binge”, which could increase the likelihood of positive symptoms (Kalayasiri et al., 2006b), compared to daily “chipping” consumption in frequent cocaine users.

The final contributor to current positive symptom severity was methadone status, whereby methadone use was associated with decreased symptom severity. In the field of organic psychoses, dual-diagnosis schizophrenia patients with opioid dependency exhibited decreases in psychiatric symptom severity over the course of methadone treatment (Cacciola et al., 2001; Marenmani et al., 2007; Pani et al., 2003). Additionally, case studies have reported reduced psychotic symptoms with methadone treatment in schizophrenia patients with concurrent opioid dependency (Brizer et al., 1985; Pacini et al., 2005; Walby et al., 2000). While the biological mechanisms underlying this effect remain unknown, a preclinical investigation reported that methadone exposure causes long term reductions in striatal dopamine D2 receptor density (Allouche et al., 2015). This indicates that methadone may directly affect dopaminergic signalling, potentially modifying the same neural substrates implicated in psychosis (Crayton et al., 1968). Farrell et al. (2002) have suggested that reductions of arousal levels from opioid use may be a proxy for the observation of an ‘antipsychotic effect’ of opioids, however, here we report a specific association between methadone and delusions – a hallmark symptom of psychosis unrelated to arousal levels.

In addition to the novel findings for positive symptoms, the present study is one of the few to address predictors of the negative symptoms presented in psychostimulant-associated psychosis. Negative symptoms are often thought of as less severe and/or prevalent in psychostimulant-associated psychosis than schizophrenia (Srisurapanont et al., 2003; Zorick et al., 2008) –

however, a more recent factor analysis found that the severity of negative symptoms of methamphetamine associated psychosis did not differ to those present in schizophrenia (Srisurapanont et al., 2011). The current results suggest that while negative symptoms may appear to be present in psychostimulant users, the severity of these symptoms are associated not with psychostimulant abuse, but rather with opioid drug effects. Thus, future studies investigating negative symptoms in polydrug users should ensure that the effects of opioids are carefully controlled for. This may help in differentially diagnosing between idiopathic psychosis and psychostimulant-associated psychosis, when prominent negative symptoms are present. Our data also suggest that the two conditions are not necessarily part of the same continuum, which has been suggested (Bramness et al., 2012).

Our approach of investigating psychosis as a continuous variable allowed us to identify risk factors pertaining to the variation within psychosis severity (van Os et al., 2014). While an approach of viewing psychosis as a categorical outcome is clinically useful for diagnostic purposes, valuable information is sacrificed with the establishment of this dichotomy. If the defined cut-off is set too low, important variation within the context of psychotic experiences will be ignored. If the cut-off is set too high, individuals presenting with mild symptoms will be unrealistically grouped with individuals experiencing no symptoms (Royston et al., 2006). Additionally, by using a continuous approach, investigations are better equipped to capture temporally pertinent relationships between variables of interest and psychosis. Though this approach does not explain why many psychostimulant users never experience a psychotic episode, it does identify the major predicting variables of the current severity of psychosis. Such an approach provides clinicians tangible targets for therapeutic intervention of acutely-ill individuals – instead of reporting vague risk factors.

Though our final linear regression model significantly predicted positive symptom severity in a psychostimulant dependent sample, the model accounted for only a modest proportion of the variation seen in symptom severity. This highlights the complexity of clinical presentation where comorbidities and multiple mediating factors may be contributing to symptom severity. In this regard, many predisposing factors beyond the scope of the study were not included here, such as genetic vulnerabilities, stress exposure, trait impulsivity, past psychotic experiences (number and duration), and sleep (Taylor et al., 2013). Additionally, self-report was a major source of the substance use data used for this study. Though general use was confirmed by a urine drug screen, current psychostimulant users may not be fully reliable sources of information for past histories of use. Also, the degree of poly-substance abuse in this population was likely a source of complex interactions and variability – though we believe that the prevalent comorbidities dealt with here are an accurate representation of the reality of living in a marginalized, urban population.

5. Conclusion

Our results suggest that the frequency of methamphetamine and marijuana use is associated with the severity of positive symptoms experienced by psychostimulant dependent individuals – while the severity of negative symptoms may be related to independent factors, such as opioid use. Additionally, an “anti-psychotic” – like effect of methadone warrants further study. Our findings may have direct and translational clinical implications, suggesting the frequency of methamphetamine and marijuana use as a tangible target for reducing current psychotic symptoms in individuals with comorbid polysubstance abuse and psychosis.

Conflicts of interest

Drs. Vila-Rodriguez, Thornton, Leonova, MacEwan, and Panenka report no competing interests. Mr(s). Willi, Gicas, Jones and Aleksic report no competing interests.

Dr. Honer has received consulting fees or sat on paid advisory boards for: In Silico, Otsuka/Lundbeck, Roche and Eli Lilly; received honoraria from Rush University, University of Ottawa, University of Calgary, University of Hong Kong, British Columbia Health Authorities, the British Association for Psychopharmacology, and the Canadian Psychiatric Association; and received Grants from the Canadian Institutes of Health Research (CIHR).

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References

- Allouche, S., Le Marec, T., Coquerel, A., Noble, F., Marie, N., 2015. Striatal dopamine D1 and D2 receptors are differentially regulated following buprenorphine or methadone treatment. *Psychopharmacology* 232, 1527–1533.
- Alam Mehrjerdi, Z., Barr, A.M., Noroozi, A., 2013. Methamphetamine-associated psychosis: a new health challenge in Iran. *Daru* 21, 1–3.
- Barr, A.M., Panenka, W.J., MacEwan, G.W., Thornton, A.E., Lang, D.J., Honer, W.G., et al., 2006. The need for speed: an update on methamphetamine addiction. *J. Psychiatry Neurosci.* 31, 301.
- Bianconi, F., Bonomo, M., Marconi, A., Kolliakou, A., Stilo, S.A., Iyegbe, C., et al., 2016. Differences in cannabis-related experiences between patients with a first episode of psychosis and controls. *Psychol. Med.* 46, 1–9.
- Binbay, T., Drukker, M., Elbi, H., Tanik, F.A., Özkunay, F., Onay, H., et al., 2012. Testing the psychosis continuum: differential impact of genetic and nongenetic risk factors and comorbid psychopathology across the entire spectrum of psychosis. *Schizophr. Bull.* 38, 992–1002.
- Brady, K.T., Lydiard, R.B., Malcolm, R., Ballenger, J.C., 1991. Cocaine-induced psychosis. *J. Clin. Psychiatry* 52, 509–512.
- Bramness, J.G., Gundersen, Ø.H., Guterstam, J., Rognli, E.B., Konstenius, M., Løberg, E. M., et al., 2012. Amphetamine-induced psychosis—a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry* 12, 221.
- Brizer, D.A., Hartman, N., Sweeney, J., Miliman, R.B., 1985. Effect of methadone plus neuroleptics on treatment-resistant chronic paranoid schizophrenia. *Am. J. Psychiatry* 142, 1106–1107.
- Caspi, A., Moffitt, T.E., Cannon, M., McClay, J., Murray, R., Harrington, H., et al., 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol. Psychiatry* 57, 1117–1127.
- Cacciola, J.S., Alterman, A.I., Rutherford, M.J., McKay, J.R., Mulvaney, F.D., 2001. The relationship of psychiatric comorbidity to treatment outcomes in methadone maintained patients. *Drug Alcohol Depend.* 61, 271–280.
- Chen, C.K., Lin, S.K., Sham, P.C., Ball, D., Loh, E.W., Hsiao, C.C., et al., 2003. Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychol. Med.* 33, 1407–1414.
- Ciccarone, D., 2011. Stimulant abuse: pharmacology, cocaine, methamphetamine, treatment, attempts at pharmacotherapy. *Prim. Care* 38, 41–58.
- Cook, C.E., 1991. Pyrolytic Characteristics, Pharmacokinetics, and Bioavailability of Smoked Heroin, Cocaine, Phencyclidine, and Methamphetamine. 1990 Census of Population and Housing: Summary population and housing characteristics. North Carolina, 115, pp. 6–23.
- Crayton, J.W., Meltzer, H.Y., Goode, D.J., 1968. The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. *Pathology* 18, 518–531.
- Degenhardt, L., Hall, W., Lynskey, M., 2003. Testing hypotheses about the relationship between cannabis use and psychosis. *Drug Alcohol Depend.* 71, 37–48.
- Emsley, R., Rabinowitz, J., Torremans, M., RIS-INT-35 Early Psychosis Global Working Group., 2003. The factor structure for the Positive and Negative Syndrome Scale (PANSS) in recent-onset psychosis. *Schizophr. Res.* 61, 47–57.

- Endicott, J., 1988. Best Estimate Clinical Evaluation and Diagnosis Form (BECED). Department of Research Assessment and Training, New York State Psychiatric Institute, New York, NY.
- Farrell, M., Boys, A., Bebbington, P., Brugha, T., Coid, J., Jenkins, R., et al., 2002. Psychosis and drug dependence: results from a national survey of prisoners. *Br. J. Psychiatry* 181, 393–398.
- Fischer, B., Rehm, J., Patra, J., Kalousek, K., Haydon, E., Tyndall, M., et al., 2006. Crack across Canada: comparing crack users and crack non-users in a Canadian multi-city cohort of illicit opioid users. *Addiction* 101, 1760–1770.
- Grant, K.M., LeVan, T.D., Wells, S.M., Li, M., Stoltenberg, S.F., Gendelman, H.E., et al., 2012. Methamphetamine-associated psychosis. *J. Neuroimmune Pharmacol.* 7, 113–139.
- Hall, W., Hando, J., Darke, S., Ross, J., 1996. Psychological morbidity and route of administration among amphetamine users in Sydney, Australia. *Addiction* 91, 81–87.
- Hambrecht, M., Häfner, H., 2000. Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective. *Aust. N.Z. J. Psychiatry* 34, 468–475.
- Henquet, C., Murray, R., Linszen, D., van Os, J., 2005. The environment and schizophrenia: the role of cannabis use. *Schizophr. Bull.* 31, 608–612.
- Kalayasiri, R., Kranzler, H.R., Weiss, R., Brady, K., Gueorguieva, R., Panhuysen, C., et al., 2006a. Risk factors for cocaine-induced paranoia in cocaine-dependent sibling pairs. *Drug Alcohol Depend.* 84, 77–84.
- Kalayasiri, R., Sughondhabirorn, A., Gueorguieva, R., Coric, V., Lynch, W.J., Morgan, P. T., et al., 2006b. Self-reported paranoia during laboratory “binge” cocaine self-administration in humans. *Pharmacol. Biochem. Behav.* 83, 249–256.
- Kalayasiri, R., Gelernter, J., Farrer, L., Weiss, R., Brady, K., Gueorguieva, R., et al., 2010. Adolescent cannabis use increases risk for cocaine-induced paranoia. *Drug Alcohol Depend.* 107, 196–201.
- Kay, S.R., Fiszbein, A., Opler, L.A., 1987. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr. Bull.* 13, 261–276.
- Kuramoto, S.J., Bohnert, A.S.B., Latkin, C.A., 2011. Understanding subtypes of inner-city drug users with a latent class approach. *Drug Alcohol Depend.* 118, 237–243.
- Lecomte, T., Mueser, K.T., MacEwan, W., Thornton, A.E., Buchanan, T., Bouchard, V., et al., 2013. Predictors of persistent psychotic symptoms in persons with methamphetamine abuse receiving psychiatric treatment. *J. Nerv. Ment. Dis.* 201, 1085–1089.
- Lichlyter, B., Purdon, S., Tibbo, P., 2011. Predictors of psychosis severity in individuals with primary stimulant addictions. *Addict. Behav.* 36, 137–139.
- Mahoney, J.J., Kalechstein, A.D., De La Garza, R., Newton, T.F., 2008. Presence and persistence of psychotic symptoms in cocaine-versus methamphetamine-dependent participants. *Am. J. Addict.* 17, 83–98.
- Mahoney, J.J., De La Garza, R., Jackson, B.J., Verrico, C.D., Ho, A., Iqbal, T., et al., 2014. The relationship between sleep and drug use characteristics in participants with cocaine or methamphetamine use disorders. *Psychiatry Res.* 219, 367–371.
- Maremmani, I., Pani, P.P., Pacini, M., Perugi, G., 2007. Substance use and quality of life over 12 months among buprenorphine maintenance-treated and methadone maintenance-treated heroin-addicted patients. *J. Subst. Abuse Treat.* 33, 91–98.
- McKetin, R., McLaren, J., Lubman, D.I., Hides, L., 2006. The prevalence of psychotic symptoms among methamphetamine users. *Addiction* 101, 1473–1478.
- McKetin, R., Lubman, D.I., Baker, A.L., Dawe, S., Ali, R.L., 2013. Dose-related psychotic symptoms in chronic methamphetamine users: evidence from a prospective longitudinal study. *JAMA Psychiatry* 70, 319–324.
- Mooney, M., Sofuoglu, M., Dudish-Poulsen, S., Hatsukami, D.K., 2006. Preliminary observations of paranoia in a human laboratory study of cocaine. *Addict. Behav.* 31, 1245–1251.
- Murray, R.M., Morrison, P.D., Henquet, C., Di Forti, M., 2007. Cannabis, the mind and society: the hash realities. *Nat. Rev. Neurosci.* 8, 885–895.
- Pacini, M., Maremmani, I., 2005. Methadone reduces the need for antipsychotic and antimanic agents in heroin addicts hospitalized for manic and/or acute psychotic episodes. *Heroin Addict. Relat. Clin. Probl.* 7, 43–48.
- Panenko, W.J., Procyshyn, R.M., Lecomte, T., MacEwan, G.W., Flynn, S.W., Honer, W. G., et al., 2013. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. *Drug Alcohol Depend.* 129, 167–179.
- Pani, P.P., Trogu, E., Carboni, G., Palla, P., Loi, A., 2003. Psychiatric severity and treatment response in methadone maintenance treatment programmes: new evidence. *Heroin Addict. Relat. Clin. Probl.* 5, 23–36.
- Power, B.D., Stefanis, N.C., Dragovic, M., Jablensky, A., Castle, D., Morgan, V., 2014. Age at initiation of amphetamine use and age at onset of psychosis: the Australian Survey of high impact psychosis. *Schizophr. Res.* 152, 300–302.
- Roncero, C., Daigre, C., Gonzalvo, B., Valero, S., Castells, X., Grau-López, L., et al., 2013. Risk factors for cocaine-induced psychosis in cocaine-dependent patients. *Eur. Psychiatry* 28, 141–146.
- Roncero, C., Comín, M., Daigre, C., Grau-López, L., Martínez-Luna, N., Eiroa-Orosa, F. J., et al., 2014. Clinical differences between cocaine-induced psychotic disorder and psychotic symptoms in cocaine-dependent patients. *Psychiatry Res.* 216, 398–403.
- Royston, P., Altman, D.G., Sauerbrei, W., 2006. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat. Med.* 25, 127–141.
- Salo, R., Nordahl, T.E., Leamon, M.H., Natsuaki, Y., Moore, C.D., Waters, C., et al., 2008. Preliminary evidence of behavioral predictors of recurrent drug-induced psychosis in methamphetamine abuse. *Psychiatry Res.* 157, 273–277.
- Satel, S.L., Edell, W.S., 1991. Cocaine-induced paranoia and psychosis proneness. *Am. J. Psychiatry* 148, 1708–1711.
- Schoeler, T., Monk, A., Sami, M.B., Klammer, E., Foglia, E., Brown, R., et al., 2016. Continued versus discontinued cannabis use in patients with psychosis: a systematic review and meta-analysis. *Lancet Psychiatry* 3, 215–225.
- Shaner, A., Roberts, L.J., Eckman, T.A., Racenstein, J.M., Tucker, D.E., Tsuang, J.W., et al., 1998. Sources of diagnostic uncertainty for chronically psychotic cocaine abusers. *Psychiatr. Serv.* 49, 684–690.
- Smith, M.J., Thirthalli, J., Abdallah, A.B., Murray, R.M., Cottler, L.B., 2009. Prevalence of psychotic symptoms in substance users: a comparison across substances. *Compr. Psychiatry* 50, 245–250.
- Sobell, M.B., Sobell, L.C., Klajner, F., Pavan, D., Basian, E., 1986. The reliability of a timeline method for assessing normal drinker college students' recent drinking history: utility for alcohol research. *Addict. Behav.* 11, 149–161.
- Srisurapanont, M., Ali, R., Marsden, J., Sunga, A., Wada, K., Monteiro, M., 2003. Psychotic symptoms in methamphetamine psychotic in-patients. *Int. J. Neuropsychopharmacol.* 6, 347–352.
- Srisurapanont, M., Arunpongpaial, S., Wada, K., Marsden, J., Ali, R., Kongsakon, R., 2011. *Prog. Neuropsychopharmacol. Biol. Psychiatry* 35, 959–964.
- Taylor, S.B., Lewis, C.R., Olive, M.F., 2013. The neurocircuitry of illicit psychostimulant addiction: acute and chronic effects in humans. *Subst. Abuse Rehabil.* 4, 29–43.
- Ujike, H., Sato, M., 2004. Clinical features of sensitization to methamphetamine observed in patients with methamphetamine dependence and psychosis. *Ann. N. Y. Acad. Sci.* 1025, 279–287.
- United Nations Office on Drugs and Crime, World Drug Report, 2014. United Nations publication, Sales No. E.14.XI.7.
- van Os, J., 2014a. The many continua of psychosis. *JAMA Psychiatry* 71, 985–986.
- van Os, J., Lataster, T., Delespaul, P., Wichers, M., Myin-Germeys, I., 2014b. Evidence that a psychopathology interactome has diagnostic value, predicting clinical needs: an experience sampling study. *PLoS One* 9 (1), e86652.
- Vergara-Moragues, E., Gómez, P.A., González-Saiz, F., Rodríguez-Fonseca, F., 2014. Cocaine-induced psychotic symptoms in clinical setting. *Psychiatry Res.* 217, 115–120.
- Vila-Rodríguez, F., Panenka, W.J., Lang, D.J., Thornton, A.E., Vertinsky, T., Wong, H., et al., 2013. The hotel study: multimorbidity in a community sample living in marginal housing. *Am. J. Psychiatry* 170, 1413–1422.
- Vorspan, F., Brousse, G., Bloch, V., Bellais, L., Romo, L., Guillem, E., et al., 2012. Cocaine-induced psychotic symptoms in French cocaine addicts. *Psychiatry Res.* 200, 1074–1076.
- Walby, F.A., Borg, P., Eikeseth, P.H., Neegaard, E., Kjerpeseth, K., Bruvik, S., et al., 2000. Use of methadone in the treatment of psychotic patients with heroin dependence. *Tidsskr. Nor. Laegeforening* 120, 195–198.
- Willi, T.S., Barr, A.M., Gicas, K., Lang, D.J., Vila-Rodríguez, F., Su, W., et al., 2016. Characterization of white matter integrity deficits in cocaine-dependent individuals with substance-induced psychosis compared with non-psychotic cocaine users. *Addict. Biol.* . <http://dx.doi.org/10.1111/adb.12363>
- Yung, A.R., Phillips, L.J., Yuen, H.P., Francey, S.M., McFarlane, C.A., Hallgren, M., 2003. Psychosis prediction: 12-month follow up of a high-risk (“prodromal”) group. *Schizophr. Res.* 60, 21–32.
- Zorick, T.S., Rad, D., Rim, C., Tsuang, J., 2008. An overview of methamphetamine-induced psychotic syndromes. *Addict. Dis. Treat.* 7, 143–156.