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ORIGINAL INVESTIGATION

A comparison of psychotic symptoms in subjects with methamphetamine versus cocaine dependence

Peter D Alexander[1] · Kristina M Gicas[2] · Taylor S Willi[2] · Clara N Kim[1] · Veronika Boyeva[3] · Ric M Procyshyn[3] · Geoff N. Smith[3] · Allen E Thornton[2] · William J Panenka[3] · Andrea A. Jones[3] · Fidel Vila-Rodriguez[3] · Donna J. Lang[4] · G William MacEwan[3] · William G Honer[3] · Alasdair M Barr[1]

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Abstract
Rationale The psychostimulant drugs cocaine and methamphetamine are potent indirect dopamine receptor agonists which act through similar but not identical mechanisms. Studies in humans have observed that a large proportion of those who chronically use these drugs experience psychotic symptoms. However, direct comparisons of psychotic symptom severity between cocaine and methamphetamine users are lacking.
Objectives The goal of the present study was to directly compare severity of psychotic symptoms between cocaine- and methamphetamine-dependent individuals. Additionally, we sought to determine how concurrent cocaine + methamphetamine dependence would influence psychotic symptoms.
Methods We recruited 153 polysubstance-using subjects meeting DSM-IV-TR criteria for cocaine dependence, 38 with methamphetamine dependence, and 32 with cocaine + methamphetamine dependence. Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) and analyzed using a five-factor model. All participants were also assessed for physical and mental illnesses as well as recent substance use. Most subjects completed a comprehensive neurocognitive battery.
Results While all three groups exhibited high total PANSS scores, the positive symptom subscale was significantly higher in the methamphetamine-dependent (17.03 ± 6.3) than the cocaine-dependent group (13.51 ± 4.12) and non-significantly higher (p = 0.08) than the cocaine + methamphetamine group (14.44 ± 5.50). Groups also differed on demographic variables, viral infection, and other indices of substance use, which were unlikely to account for the difference in positive symptoms. There were only modest differences between groups in neurocognitive function.
Conclusions Methamphetamine dependence was associated with more severe positive symptoms of psychosis than cocaine dependence. Concurrent cocaine + methamphetamine dependence did not increase psychosis severity.

Keywords Cocaine · Dependence · Methamphetamine · Neurocognition · PANSS · Psychosis · Psychostimulant · Substance use · Symptom severity

Introduction

The psychostimulant drugs represent a diverse class of psychoactive compounds that share in common the capacity to activate the central nervous system and modify behavior (Barr and Markou 2005; Barr et al. 2002) Two of the most common and powerful drugs in this class include cocaine and methamphetamine. Both drugs cause a rapid and sustained increased in synaptic levels of central monoamines, with a particularly potent effect on the mesolimbic dopamine pathway, which likely underlies their significant abuse potential (Leshner and Koob 1999). Although these compounds function as indirect dopamine agonists, there are significant differences between the two, both in terms of mechanism of action, as well as in pharmacokinetics (reviewed in Barr et al. 2006; Panenka et al. 2013). Both drugs

✉ Alasdair M Barr
al.barr@ubc.ca

[1] Department of Pharmacology, 2176 Health Sciences Mall, University of British Columbia, Vancouver, B.C. V6T 1Z3, Canada

[2] Department of Psychology, Simon Fraser University, Burnaby, B.C. V5A 1S6, Canada

[3] Department of Psychiatry, University of British Columbia, Vancouver, B.C. V6T 1Z3, Canada

[4] Department of Radiology, University of British Columbia, Vancouver, B.C. V6T 1Z3, Canada

increase synaptic dopamine levels by blocking the plasmalemmal dopamine transporter (DAT) and preventing reuptake of impulse-dependent dopamine release. However, amphetamines additionally increase synaptic dopamine levels via the DAT by causing cytosolic dopamine to be reverse transported outside the cell (Fleckenstein et al. 2007) and may create conformational changes in the DAT (Kahlig et al. 2005) allowing cytosolic dopamine to escape. Amphetamines also cause the direct release of dopamine from presynaptic vesicles, possibly by their activity as weak bases (Fleckenstein et al. 2007 but see Hondebrink et al. 2009), and prevent reuptake of dopamine into presynaptic vesicles by binding competitively to the VMAT-2 vesicular transporter (Schwartz et al. 2006). In vivo animal studies have demonstrated that methamphetamine is a more potent releaser of dopamine than cocaine at equivalent concentrations (Izawa et al. 2006; Mach et al. 1997). Methamphetamine also has a significantly longer elimination half-life than cocaine (8–13 vs 1–3 h, respectively) (Busto et al. 1989) and a slower clearance from brain (Fowler et al. 2008), resulting in longer lasting behavioral and psychological effects.

Acute ingestion of either cocaine or methamphetamine initially results in affective and cognitive changes, including increased energy, elevated mood, greater sociability, and euphoria (Bershad et al. 2015; Kalapatapu et al. 2012; Wachtel et al. 2002). However, with increasing doses or duration of ingestion, additional dysphoric effects become prominent. With sufficient drug exposure, a significant proportion of individuals develop symptoms that result in a lasting syndrome referred to as "psychostimulant induced psychosis," which symptomatically resembles schizophrenia spectrum disorders (Alam Mehrjerdi et al. 2013; Angrist et al. 1974; Lecomte et al. 2013; Medhus et al. 2013). Approximately 50–75% of cocaine users (Brady et al. 1991; Mooney et al. 2006; Satel and Edell 1991; Smith et al. 2009; Vergara-Moragues et al. 2012; Vorspan et al. 2012) and 50–60% of methamphetamine users (Grant et al. 2012; McKetin et al. 2006; Smith et al. 2009) experience psychotic symptoms during or after drug ingestion. Drug effects are characterized by both positive (hallucinations, delusions, disorganized thinking) and negative (flattened affect, emotional withdrawal, lack of spontaneity) symptoms. Deficits in neurocognitive function similar to those noted in schizophrenia have also been reported in methamphetamine-induced psychosis (Jacobs et al. 2008).

At present, there is a limited body of evidence that directly compares the phenomenology of psychosis between cocaine and methamphetamine users in non-schizophrenia spectrum individuals. Given the above differences between the two drugs, there is justification for examining whether psychotic symptoms present differently between cocaine and methamphetamine users. One inpatient study of 19 cocaine- and methamphetamine-dependent subjects (Harris and Batki 2000), most of whom were treated with antipsychotics, reported very high Positive and Negative Syndrome Scale (PANSS) positive symptom scores (a group mean of 30), but no direct comparison was made between cocaine and methamphetamine users. A study of 503 prisoners (Farrell et al. 2002) observed a slightly higher rate of psychosis in cocaine-dependent (21.3%) versus methamphetamine-dependent (18.1%) individuals, but no measure of psychosis severity was provided. Perhaps the most comprehensive study to date on this topic compared psychosis in 42 cocaine-dependent and 43 methamphetamine-dependent subjects (Mahoney et al. 2008), using the Psychotic Symptom Assessment Scale. The study observed a greater frequency of select psychotic symptoms in methamphetamine users, although symptom severity again was not provided, leaving open the question as to whether symptoms were equally as severe in both groups. With the existing literature in mind, the goal of the present study was therefore to directly compare psychotic symptoms in polysubstance-using cocaine and methamphetamine-dependent subjects using the PANSS. This test instrument provides a comprehensive and quantitative index of psychotic symptom severity (Kay et al. 1987) with high construct validity (Kay et al. 1988), high internal reliability (Peralta and Cuesta 1994), and good sensitivity to change in psychotic symptoms (Lindenmayer et al. 1986), resulting in its widespread use for measuring psychotic symptoms in schizophrenia and other forms of psychosis. We also included a group of subjects who were both cocaine *and* methamphetamine dependent, to determine how the two drugs would interact to affect psychotic symptoms. In addition to measuring psychosis, we also measured neurocognitive function, to determine whether putative differences between groups reflected psychosis in particular, or a broader effect on brain function.

Materials and methods

Study population

Subjects were recruited from Single Room Occupancy (SRO) hotels and the Downtown Community Court (DCC) in the Downtown Eastside neighborhood of Vancouver, Canada. All subjects were selected from the ongoing Hotel Study, which is an observational longitudinal cohort study of multimorbidity in a marginalized population (Jones et al. 2015; Jones et al. 2013; Vila-Rodriguez et al. 2013). For this cohort, we excluded all cases of past or present schizophrenia and schizoaffective disorder. From the remaining participants, inclusion criteria were current cocaine dependence, methamphetamine dependence, or both (DSM-IV-TR criteria), fluency in English, ability to provide informed consent, and an available PANSS baseline assessment; concurrent treatment with antipsychotic drugs was not exclusionary. To be consistent with our previous studies (Willi et al. 2016a), and to decrease variability in cognitive testing, we also excluded all

subjects 60 or more years of age. 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 and received a modest honorarium for their time.

Measures

Detailed information about demographic indices was collected, including age, gender, ethnicity, and education. Blood samples were drawn for testing at the British Columbia Centre for Disease Control, which included serology for the human immunodeficiency virus (HIV); seropositivity for HIV indicates current infection. General physical health was assessed with the Short Form 36 (SF-36) Health Survey, which is a brief self-administered questionnaire that generates scores across eight dimensions of health and is widely used for diverse patient groups (McHorney et al. 1994). To ascertain psychiatric diagnoses, the Mini-International Neuropsychiatric Interview was administered, as well as a psychiatric assessment which was conducted by a psychiatrist. Diagnoses of psychiatric disorders and substance dependency (over the past 12 months) were made according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (APA 2000), by an experienced psychiatrist (WGH, OL, or FV-R) through consensus evaluation with the Best Estimate Clinical Evaluation and Diagnosis (BECED) (Endicott 1988). Drug use was recorded by a trained research assistant for the 28 days prior to the psychiatric assessment with the Time Line Follow Back method (TLFB; Sobell et al. 1986), which was corroborated with a urine drug screen when possible. Duration of regular drug use and the age of first use for the major classes of drugs were provided by self-report. Nicotine dependence was measured using the Fagerstrom Test for Nicotine Dependence.

The severity of psychosis was assessed with the full 30-item PANSS (Kay et al. 1987), which has been used previously in unstably housed populations (Tsai et al. 2011). Data from the PANSS were analyzed according to both the standard three-factor as well as the five-factor models (Emsley et al. 2003). For the latter, individual items on the PANSS were grouped into the following factors and summed: *positive dimension* (PANSS items P1, P3, P5, P6, G9, and G12), *negative dimension* (N1, N2, N3, N4, N6, G7, G13, and G16), *disorganization dimension* (P2, N5, N7, G5, G10, G11, and G15), *excitement dimension* (P4, P7, G8, and G14), and *anxiety/depression dimension* (G1, G2, G3, G4, and G6) (Emsley et al. 2003).

Neurocognition

Neuropsychological tests were administered by trained researchers under the supervision of a registered psychologist, as described previously (Gicas et al. 2016; Gicas et al. 2014), using a test battery that we have previously implemented in this population (Tang et al. 2015). Subjects were not tested if they exhibited obvious signs of drug intoxication or recent alcohol use. Time of most recent cigarette was not collected. Premorbid IQ was estimated using the Wechsler Test of Adult Reading (WTAR; Wechsler 2001). Verbal learning was assessed with the immediate recall score of the Hopkins Verbal Learning Test-Revised (HVLT; Brandt and Benedict 2001). The Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray et al. 1996) was used to determine sustained attention via the Rapid Visual Information Processing subtest, while mental flexibility was assessed with the intra-dimensional/extra-dimensional subtest. Cognitive inhibition was measured using the Color-Word trial from the Stroop Color-Word Test. Affective decision-making was determined using the total net score from the Iowa Gambling Task (IGT; Bechara et al. 1994).

Analysis

Data were analyzed using SPSS software version 24 (SPSS Inc., IBM Corp., Armonk, USA). Descriptive statistics were calculated and plotted for variables, and normality of psychosis outcome variables was tested using the Kolmogorov-Smirnov test. Group differences were determined using one-way analysis of variance (ANOVA) for continuous variables, while the non-parametric Kruskal-Wallis test was used to compare non-normal psychosis outcome variables. An analysis of covariance (ANCOVA) was used to examine group differences on neurocognitive variables to adjust for the effect of age. Chi-squared analyses were employed for categorical data; LSD post hoc tests were used to examine sources of specific differences. The alpha level was set to 0.05.

Results

Descriptive

A total of 223 participants met inclusion criteria and were investigated in this analysis, which included 153 subjects with cocaine dependence, 38 with methamphetamine dependence and 32 with concurrent cocaine + methamphetamine dependence, based on DSM-IV TR diagnostic criteria. Table 1 describes the sociodemographic, clinical, and substance use characteristics of the sample. For all three groups, participants were mainly early middle-aged males with an incomplete high school education. Gender frequency did not differ between groups. However, there was a notable difference in age between the three groups ($F_{2, 222} = 26.51$, $p < 0.001$), with the cocaine-dependent subjects (44.8 ± 7.9 years) being significantly older than both the methamphetamine-dependent (34.4 ± 10.4 years) and cocaine + methamphetamine-dependent (38.4 ± 8.1 years) groups. Highest level of education was similar between groups, and ethnicity was also consistent across groups, with most subjects self-reporting as

Table 1 Sociodemographic, clinical, and substance use characteristics of the population

	Cocaine (n = 153)		Meth (n = 38)		Cocaine + meth (n = 32)			
	Mean (SD)	% (n/N)	Mean (SD)	% (n/N)	Mean (SD)	% (n/N)	Test statistic[a]	p value
Gender (F)		24.3% (37/152[b])		21.1% (8/38)		40.6% (13/32)	4.24	0.120
Age (years)	44.78 (7.93)		34.42 (10.44)		38.44 (8.14)		26.51	*<0.001*
Education (years)	10.29 (2.56)		10.66 (2.08)		10.13 (2.66)		0.46	0.635
Ethnicity		59.4% (91/153)		55.0% (22/38)		60.0% (18/32)	2.31	0.679
White		28.1% (43/153)		32.5% (13/38)		40.0% (12/32)		
Aboriginal		12.4% (19/153)		7.5% (3/38)		6.7% (2/32)		
Other								
Relationships		67.8% (103/152)		55.3% (21/38)		43.8% (14/32)	8.92	0.063
Married/partner		14.5% (22/152)		13.2% (5/38)		25.0% (8/32)		
Separated		17.8% (27/152)		31.6% (12/38)		31.3% (10/32)		
Divorced								
HIV positive		21.5% (32/149)		3.0% (1/33)		25.8% (8/31)	6.92	*0.031*
SF-36	43.84 (10.10)		46.80 (10.80)		45.19 (10.67		1.12	0.327
Bipolar type I		5.2% (8/153)		5.3% (2/38)		6.3% (2/32)	0.05	0.973
Bipolar type II		2.0% (3/153)		5.3% (2/38)		0.0% (0/32)	2.37	0.306
Major depression		13.7% (21/153)		15.8% (6/38)		15.7% (5/32)	0.16	0.925
Alcohol dependence		20.3% (31/153)		2.6% (1/38)		15.6% (5/32)	6.86	*0.032*
Cannabis dependence		26.1% (40/153)		39.5% (15/38)		50.0% (16/32)	8.17	*0.017*
Heroin dependence		43.4% (66/152)		47.4% (18/38)		62.5% (20/32)	3.87	0.144
Alcohol	12.70 (3.86)		12.68 (3.04)		13.59 (4.67)		0.73	0.481
Age of first use (years)								
Cannabis	13.45 (3.00)		13.13 (2.89)		13.32 (3.13)		0.18	0.839
Age of first use (years)								
Opioids	24.08 (9.91)		23.43 (9.38)		20.45 (6.77)		1.78	0.171
Age of first use (years)								
Cocaine	22.18 (8.54)		17.94 (4.87)		18.25 (5.20)		6.63	*0.002*
Age of first use (years)								
Amphetamines	23.08 (9.72)		22.21 (9.81)		24.53 (12.17)		0.46	0.633
Age of first use (years)								
TLFB alcohol days used	3.96 (8.01)		1.34 (3.49)		3.59 (8.32)		1.86	0.157
TLFB alcohol dose[c] (units)	7.44 (9.71) (n = 67)		5.37 (12.45) (n = 16)		6.84 (7.78) (n = 12)		0.28	0.758
TLFB cannabis days used	6.07 (10.56)		11.79 (12.13)		11.63 (13.05)		6.09	*0.003*
TLFB cannabis dose[c] (g)	0.87 (0.81) (n = 59)		1.26 (1.42) (n = 24)		1.65 (1.76) (n = 16)		3.16	*0.047*
TLFB heroin days Used	5.21 (9.54)		7.21 (10.86)		11.47 (12.11)		5.15	*0.007*
TLFB heroin dose[c] (g)	0.38 (0.43) (n = 53)		0.21 (0.25) (n = 16)		0.35 (0.54) (n = 21)		1.02	0.365
TLFB crack cocaine days used	13.16 (11.24)		0.37 (1.26)		9.75 (12.25)		23.00	*<0.001*
TLFB crack cocaine dose[c] (g)	0.69 (0.90) (n = 118)		0.28 (0.43) (n = 5)		2.06 (6.60) (n = 18)		2.56	0.081

Table 1 (continued)

	Cocaine (n = 153)		Meth (n = 38)		Cocaine + meth (n = 32)			
	Mean (SD)	% (n/N)	Mean (SD)	% (n/N)	Mean (SD)	% (n/N)	Test statistic[a]	p value
TLFB powder cocaine days used	3.79 (8.54)		0.05 (0.32)		1.19 (5.10)		4.81	*0.009*
TLFB powder cocaine dose[c] (g)	0.38 (0.42) (n = 39)		0.50 (n = 1)		0.23 (0.19) (n = 4)		0.33	0.721
TLFB meth days used	0.03 (0.23)		12.29 (9.17)		7.28 (10.40)		88.57	*< 0.001*
TLFB meth dose[c] (g)	0.08 (0.03) (n = 2)		0.27 (0.32) (n = 34)		0.37 (0.67) (n = 18)		0.51	0.606
Fagerstrom Test for Nicotine Dependence	4.06 (2.37)		3.78 (2.26)		3.30 (2.04)		1.42	0.244
Route of administration of primary drug:		20.4% (31/152)		65.8% (25/38)		53.1% (17/32)	35.33	*< 0.001*
IV		79.6% (121/152)		34.2% (13/38)		46.9% (15/32)		
Inhalation								

[a] Test statistic either refers to a t-value, F-ratio, or a chi-squared value

[b] One transgender subject was excluded from this analysis

[c] Daily dose only includes subjects in analysis who consumed the drug in previous 28 days

P values in italics significant at p < 0.05

either "white" (58.7%) or "aboriginal" (30.5%). The groups differed in relationship status, an effect that was marginally significant (χ^2 (4) = 8.92, p = 0.062), with cocaine-dependent subjects most likely, and cocaine + methamphetamine-dependent subjects least likely, to be married or in a long-term relationship with a partner.

Psychiatric and medical comorbidities

With regard to HIV infection, there was a clear difference between the three groups (χ^2 (2) = 6.92, $p < 0.05$), as the cocaine-dependent (21.5%) and cocaine + methamphetamine-dependent (25.8%) groups exhibited significantly higher rates of infection than the methamphetamine-dependent (3.0%) group. Despite group differences in rates of infection for HIV, there were no differences in self-reported global physical health, as measured by the SF-36. In terms of psychiatric comorbidities, the groups did not differ significantly in rates of severe mental illness, including bipolar I, bipolar II disorder, and major depressive disorder. Eleven subjects in the study were prescribed benzodiazepines (diazepam, clonazepam, triazolam, oxazepam, and temazepam), including nine in the cocaine-dependent group and one in each of the other two groups.

Substance use

In this population, other forms of drug use were common, and consistent with the patterns of substance use observed in other inner-urban environments, where many marginalized individuals engage in polysubstance use, yet tend to have preferred drugs on which they remain dependent over the longer term (Kuramoto et al. 2011). Regarding drug dependence, there was a group difference in the rate of alcohol dependence (χ^2 (2) = 6.86, $p < 0.05$), which was higher in the cocaine dependent (20.3%) and cocaine + methamphetamine-dependent (15.6%) groups than the methamphetamine-dependent (2.6%) group. Cannabis dependence also differed (χ^2 (2) = 8.17, $p < 0.05$), whereby rates of cannabis dependence were significantly higher in the cocaine + methamphetamine-dependent (50.0%) group than the cocaine-dependent (26.1%) group, while the methamphetamine-dependent (39.5%) group did not differ significantly from either of the other two groups. Age of first use of most of the major classes of drugs, including alcohol, cannabis, amphetamines, and opioids did not differ between groups. Of interest, the one drug where age of first use did differ was cocaine ($F_{2, 217}$ = 6.63, $p < 0.005$), whereby age of first use in the cocaine-dependent (22.2 ± 8.5 years) group was significantly older than either the methamphetamine- (17.9 ± 4.9 years) or cocaine + methamphetamine-dependent (18.3 ± 5.2 years) group.

Data from the TLFB (Table 1) indicated that subjects used a variety of different drugs. Consistent with their diagnosis of dependence, both the cocaine- (13.2 ± 11.2 days) and cocaine + methamphetamine-dependent (9.8 ± 12.3 days) groups used crack

cocaine on a regular basis, with the latter group using the drug less often, but with a significantly higher dose; crack cocaine use was minimal in the methamphetamine-dependent group (0.4 ± 1.3 days). Powder cocaine use also exhibited a group difference ($F_{2, 222} = 4.81$, $p < 0.01$) as the cocaine-dependent group used the drug significantly more frequently (3.4 ± 8.5 days) than the methamphetamine-dependent (0.1 ± 0.3 days) group and showed a non-significant trend ($p = 0.070$) to use it more often than the cocaine + methamphetamine-dependent (1.2 ± 5.1 days) group. Conversely, there was a group effect of methamphetamine use ($F_{2, 222} = 88.57$, $p < 0.001$), in which all groups differed significantly from each other, with the methamphetamine-dependent (12.3 ± 9.2 days) group using the drug more often than either the cocaine + methamphetamine-dependent (7.3 ± 10.4 days) group or the cocaine-dependent (0.03 ± 0.2 days) group. Heroin use differed between groups ($F_{2, 222} = 5.15$, $p < 0.01$), with the cocaine + methamphetamine-dependent (11.5 ± 12.1 days) group using the drug significantly more often than the cocaine-dependent (5.2 ± 9.5 days) group and non-significantly more often ($p = 0.081$) than the methamphetamine-dependent (7.2 ± 10.9 days) group. Cannabis use also differed significantly ($F_{2, 222} = 6.09$, $p < 0.005$), with cocaine-dependent (6.1 ± 10.6 days) subjects using the drug significantly less often than either the methamphetamine-dependent (11.8 ± 12.1 days) or cocaine + methamphetamine-dependent (11.6 ± 13.0 days) subjects. The amount of cannabis used per day was also significantly higher in the cocaine + methamphetamine-dependent (1.7 ± 1.8 g) group than the cocaine-dependent (0.9 ± 0.8 g) group. Route of drug administration was also compared between groups, in which the primary drug of use was included (i.e., cocaine for cocaine-dependent subjects, methamphetamine for methamphetamine-dependent subjects, and whichever drug was used more commonly in the cocaine + methamphetamine-dependent subjects). The analysis indicated that IV drug use was significantly more common (χ^2 (2) = 35.3, $p < 0.001$) in the methamphetamine-dependent (65.8%) and cocaine + methamphetamine-dependent (53.1%) groups than the cocaine-dependent group (20.4%). No users were exclusive intranasal users.

As previous studies have demonstrated that severity of psychostimulant dependence is significantly associated with risk for developing positive symptoms, such as paranoia (Kalayasiri et al. 2006a), we compared the number of days in the previous month that subjects used either cocaine (either crack or powder) or methamphetamine, which has previously been associated with dependence severity (Gossop et al. 1995). The cocaine + methamphetamine-dependent group used drugs most commonly (18.2 ± 15.7 days), followed by the cocaine-dependent group (17.0 ± 13.7 days) and lastly the methamphetamine-dependent group (12.7 ± 9.3 days); however, the groups did not differ significantly on this measure ($F_{2, 222} = 1.88$, NS), suggesting that—based on this proxy index, but consistent with prior studies—the three groups showed a similar severity of dependence.

Psychosis

Data from the PANSS were first analyzed according to the traditional three-factor model (Kay et al. 1987). Mean total PANSS scores for the three groups ranged from 65.63 ± 14.52 in the cocaine-dependent group to 69.91 ± 14.89 for the cocaine + methamphetamine-dependent group and 70.76 ± 15.29 in the methamphetamine-dependent group; there was a non-significant trend for a group effect ($F_{2, 222} = 2.53$, $p = 0.082$). Individual total PANSS scores ranged from 37 to 111, with a minimum total PANSS score for any subject of 37 in the cocaine-dependent group, 44 for the cocaine + methamphetamine-dependent group, and 50 in the methamphetamine-dependent group. There was no group difference in general psychopathology or the positive and negative subscales, of which the latter two were non-normally distributed. For the five-factor PANSS (Table 2), data for all subscales were non-normally distributed and therefore subject to non-parametric testing. Individual item scores are provided in Fig. 1. Results indicated a significant group effect (χ^2 (2) = 10.06, $p < 0.01$) for the PANSS positive subscale, whereby the positive subscale was significantly greater in the methamphetamine-dependent (17.03 ± 6.26) group than the cocaine-dependent (13.51 ± 4.12) group, and non-significantly higher ($p = 0.077$) than the cocaine + methamphetamine-dependent (14.44 ± 5.50)

Table 2 Descriptive statistics and group differences for five-factor PANSS subscales

	Cocaine (n = 153) Mean (SD)	Meth (n = 38) Mean (SD)	Cocaine + meth (n = 32) Mean (SD)	Test statistic[a]	p value
Five-factor PANSS positive subscale	13.51 (4.12)	17.03 (6.26)	14.44 (5.50)	10.06	*0.007*
Five-factor PANSS negative subscale	16.60 (6.10)	17.79 (6.32)	17.34 (5.37)	1.50	0.473
Five-factor PANSS disorganization subscale	15.26 (5.03)	16.13 (5.17)	16.75 (5.67)	2.80	0.247
Five-factor PANSS excitement subscale	7.99 (3.30)	7.26 (2.27)	8.43 (2.98)	1.93	0.380
Five-factor PANSS anxiety/depression subscale	12.64 (3.88)	12.55 (3.96)	13.03 (3.81)	0.35	0.841

[a] Test statistic refers to a chi-squared value

P values in italics significant at $p < 0.05$

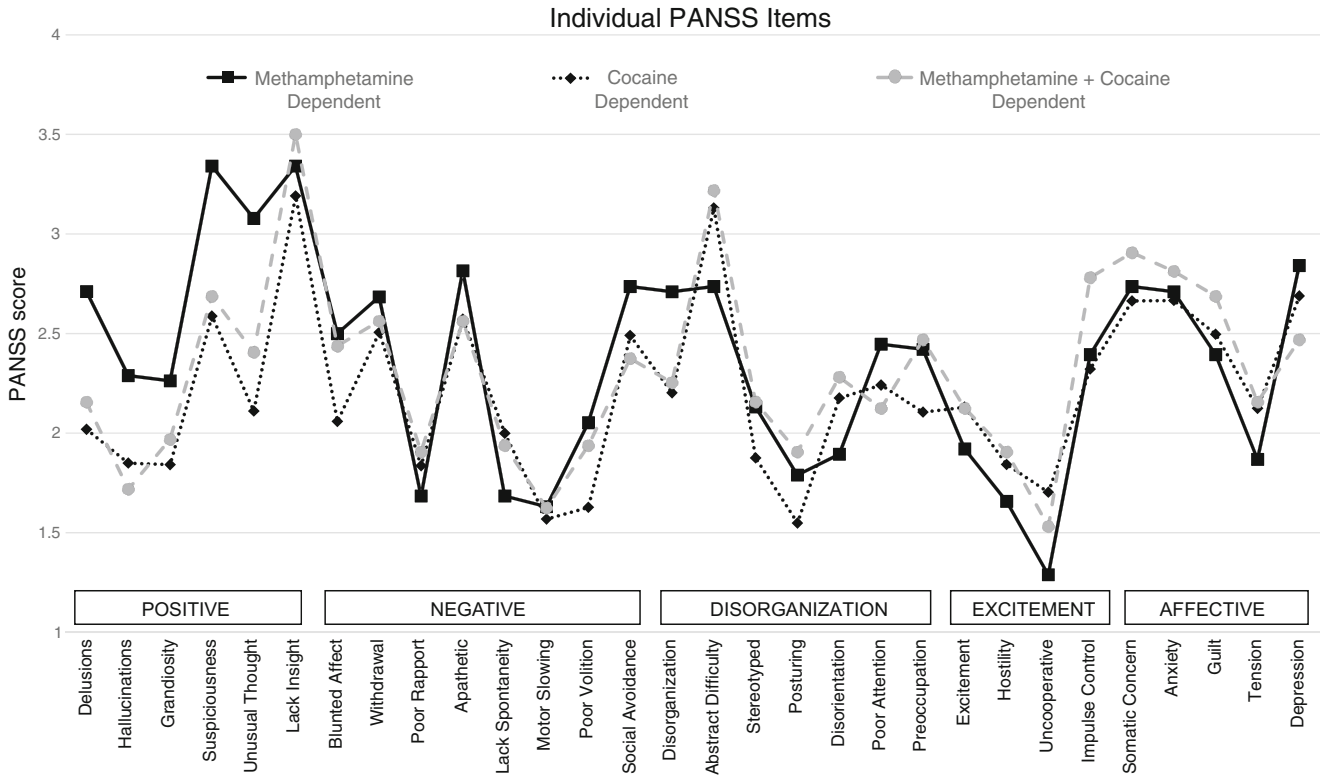

Fig. 1 Individual 30-item PANSS scores for cocaine-, methamphetamine-, and cocaine + methamphetamine-dependent groups. Individual PANSS items arranged according to the five-factor model (Emsley et al. 2003)

group. A follow-up ANCOVA, including age and route of drug administration as covariates, confirmed that the effect of both covariates were not significant, and groups remained significantly different from each other ($F_{2,\ 217} = 3.05$, $p < 0.05$) when including either or both covariates. Closer examination of the individual items in the 5 factor PANSS positive subscale revealed that the difference between the cocaine versus the methamphetamine-dependent groups was most evident (≥0.7 point group mean difference) in items including greater delusions, suspiciousness and unusual thought content, with moderate effects (0.4–0.7 point group mean difference) of hallucinations and grandiosity, and minimal difference in lack of insight, which was the highest scored item for all three groups. The groups did not differ significantly in any of the other four factors of the five-factor PANSS. To determine whether recent drug use accounted for differences in psychotic symptom severity, we compared PANSS subscale scores in subjects who had used their drug of dependence in the past 28 days ($n = 192$) versus not ($n = 30$), based on data from the TLFB. There was no difference in positive symptoms (14.14 ± 4.76 vs 14.90 ± 5.84), with the only group difference evident for anxiety/depression symptoms which was significantly higher ($p = 0.01$) in the group which had not used drugs in the past 28 days (14.37 ± 4.15 vs 12.41 ± 3.77). Similar results were evident when only the past two weeks of drug use was examined, except that the effect on anxiety/depression symptoms was no longer significant ($p = 0.11$).

Cognition

To characterize the neurocognitive functioning of the overall sample, T-scores (mean = 50, SD = 10) were calculated using available normative data adjusted for age and/or education (see Table 3). Estimated premorbid IQ, inhibition, and decision-making, scores fell in the average range. Verbal memory was the most impaired domain (>1.5 SD below the mean), while milder impairments were observed for attention and mental flexibility (>1 SD below the mean). Results of the ANCOVA (Table 3) indicated that only premorbid Full Scale IQ (WTAR scores) significantly differed between groups, with higher scores in the methamphetamine-dependent group (99.72 ± 8.16) compared to the cocaine-dependent (96.56 ± 8.93) and the cocaine + methamphetamine-dependent groups (94.56 ± 9.93) ($F_{2,\ 217} = 3.49$, $p < 0.05$). A non-significant trend was observed for inhibition (Stroop Color-Word scores) ($F_{2,\ 210} = 2.53$, $p = 0.082$), with higher scores in the methamphetamine-dependent group (40.53 ± 10.38), compared to the cocaine-dependent (35.52 ± 9.51) and cocaine + methamphetamine-dependent groups (34.81 ± 10.54). No other significant group differences were observed ($p > 0.05$).

A follow-up analysis was conducted to explore the relationship between neurocognitive functioning and the five-factor PANSS subscales in the entire cohort using a series of Pearson correlations. Significant negative associations were observed

Table 3 Descriptive statistics and group differences for neurocognitive variables

	Mean T-score	Cocaine (n = 153) Mean (SD)	Meth (n = 38) Mean (SD)	Cocaine + meth (n = 32) Mean (SD)	Test statistic[a]	p value
Premorbid FSIQ	47.86	96.56 (8.93)	99.72 (8.16)	94.56 (9.93)	3.49	*0.032*
Verbal memory	31.74	19.59 (5.39)	21.59 (4.23)	19.17 (4.94)	1.44	0.239
Attention	37.79	0.86 (0.06)	0.88 (0.06)	0.87 (0.05)	1.62	0.202
Inhibition	50.00	35.52(9.51)	40.53 (10.38)	34.81 (10.54)	2.53	0.082
Mental flexibility	37.45	57.21 (43.18)	48.33 (49.82)	52.21 (40.15)	0.01	0.996
Decision-making	44.35	-8.38 (32.59)	5.53 (29.24)	-0.67 (35.94)	2.33	0.100

Mean T-scores reflect demographically corrected scores based on normative data for individual neurocognitive tests. Means and standard deviations were reported using raw data, but these values were adjusted for age in the ANCOVA

[a] Test statistic represents F-ratio from ANCOVA

P values in italics significant at $p < 0.05$

between the disorganized factor and premorbid IQ ($r = -0.16$, $p < 0.05$), inhibition ($r = -0.24$, $p < 0.001$), verbal memory ($r = -0.18$, $p = 0.05$), and attention ($r = -0.37$, $p < 0.001$), as well as between the negative factor and attention ($r = -0.16$, $p < 0.05$). No significant correlations were observed between neurocognitive scores and positive, excitement or anxiety/depression factors ($p > 0.10$).

While subjects who exhibited acute signs of drug intoxication were not given neurocognitive tests, a considerable number of subjects were positive on the urine drug screen for amphetamines (21.5%), cocaine (72.2%), cannabis (35.9%), and opiates (38.6%).

Discussion

In the present study, we compared severity of psychotic symptoms, as measured by the PANSS, in three polysubstance-using groups, who were either cocaine dependent, methamphetamine dependent, or cocaine + methamphetamine dependent. In general, the severity of psychosis in all three groups was high. When compared using the standard three-factor model (positive, negative, and general psychopathology subscales) (Kay et al. 1987), there was no significant difference between the three groups. However, when using a five-factor model (Emsley et al. 2003) (positive, negative, disorganization, excitement, and anxiety/depression), there was a large and highly significant difference in the PANSS positive factor, in which the methamphetamine group presented with more severe psychotic symptoms than the cocaine-dependent group, and non-significantly more severe psychotic symptoms than the cocaine + methamphetamine- dependent group. In parallel, we concurrently assessed neurocognitive performance in the same subjects. The cohort as a whole performed below average on measures of verbal memory, attention, and mental flexibility, but differed significantly between groups only in premorbid IQ, in which the methamphetamine-dependent group performed marginally better than the other two groups.

In addition to differing on the positive symptoms of psychosis, the groups also varied on a number of other factors. The cocaine-dependent group was substantially older than the other two groups and had lower rates of cannabis dependence and cannabis use, whereas the methamphetamine-dependent group was the youngest, had lowest rates of HIV infection and the lowest rate of alcohol dependence, while the cocaine + methamphetamine-dependent group had the highest rates of heroin dependence and heroin use. The methamphetamine-dependent group used significantly more methamphetamine than both other groups. Otherwise, groups did not differ in self-reported physical health, based on scores from the SF-36, or in the prevalence of other forms of severe mental illness. Groups also did not differ on the number of days of cocaine (either crack or powder) or methamphetamine used in the previous month, which has previously been associated with dependence severity for both drugs (Gossop et al. 1995).

The current findings are, to our knowledge, the first direct comparison of psychosis severity between non-schizophrenia spectrum cocaine- and methamphetamine-dependent individuals. The inclusion of a group with both cocaine + methamphetamine dependence also represents a novel comparison. Previous studies have provided valuable insights into psychosis in cocaine and methamphetamine users, but have predominantly focused on comparing the prevalence of psychosis or specific symptoms in these two groups rather than symptom severity itself (Farrell et al. 2002; Mahoney et al. 2010; Vallersnes et al. 2016). We have recently studied psychostimulant-induced psychosis in this population (Willi et al. 2016b), and it is apparent that evaluating psychosis along a continuum, such as by using the PANSS, can result in important differences in outcome results than when subjects are categorized in a binary manner as being "psychotic or not." The latter approach can be prone to arbitrary cutoff values for

inclusion that can ignore valuable information about subthreshold symptoms. Nevertheless, the current findings are consistent with several previous studies in which positive symptoms are exacerbated in methamphetamine users. In one study that used the PANSS, positive subscale scores (three-factor model) were relatively high compared to negative and general psychopathology subscale scores in a cohort of 14 amphetamine and 5 cocaine users who met DSM-IV criteria for amphetamine- or cocaine-induced psychotic disorder (Batki and Harris 2004; Harris and Batki 2000); however, scores were not compared between drug classes. Of interest in the studies by Batki and Harris, auditory hallucinations, bizarre and persecutory delusions were especially common in this group which consisted predominantly of amphetamine users, and which may resemble the more severe delusions, hallucinations, suspiciousness, and unusual thought content in the current methamphetamine-dependent group. Indeed, studies of methamphetamine-dependent subjects report that paranoid and persecutory delusions are a particularly common symptom (Bousman et al. 2015). This selective increase in paranoid and unusual thought content symptoms in methamphetamine users may underlie the greater sensitivity of the five-factor PANSS to detect differences in the positive subscale, as this particular cluster of symptoms is weighted more heavily than in the five-factor model.

Arguably, the simplest explanation for the difference in positive symptom severity in methamphetamine-dependent compared to cocaine-dependent subjects is that it reflects pharmacodynamic and pharmacokinetic differences between the two drugs, and their ability to modify mesolimbic dopamine levels, which are posited to underlie the positive symptoms of idiopathic psychosis (Abi-Dargham 2014). In vivo preclinical studies in rodents using cerebral microdialysis have demonstrated that acute methamphetamine doses approximately one order of magnitude lower than those of cocaine can increase synaptic dopamine levels in the nucleus accumbens equivalently (Izawa et al. 2006), with even relatively low single doses of methamphetamine increasing dopamine levels 1000–2000% above baseline (Camp et al. 1994). Perhaps of more relevance to the present study, lower binge-like doses of methamphetamine (Segal and Kuczenski 1997b) than cocaine (Segal and Kuczenski 1997a) in rats are required to induce behavioral alterations homologous to those observed in human psychosis. Extrapolation of preclinical research to the current human cohort is confounded by numerous factors, including route of administration among others (Matsumoto et al. 2002), but it is likely that methamphetamine's more potent effect on central catecholamines is a significant factor in its greater psychotogenic properties. The significantly longer half-life of methamphetamine than cocaine (8–13 vs 1–3 h, respectively) (Busto et al. 1989) could also contribute to greater psychosis in the methamphetamine users. Both the cocaine- and methamphetamine-dependent groups used their drug a similar number of days each month, so levels of methamphetamine, with its substantially longer half-life, would be expected to remain at physiologically active levels for longer, resulting in more sustained activation of mesolimbic dopamine pathways. However, alternative explanations are possible for the difference in psychosis between methamphetamine- and cocaine-dependent subjects. It is unlikely that demographic or immune variables including age and HIV infection would account for the greater positive symptoms in the methamphetamine-dependent group, as subjects in this group were younger, and had notably lower rates of HIV infection, all of which should result in greater neural reserve (Fornito et al. 2015). It is possible that concurrent substance use could contribute to differences in psychosis severity, as the cocaine-dependent group had higher rates of alcohol dependence and lower rates of cannabis dependence than the methamphetamine group. Cannabis, in particular, could further increase positive symptoms in psychostimulant users (McKetin et al. 2013; Willi et al. 2016b), but this would not account for the lower positive symptoms in the cocaine + methamphetamine-dependent group, who had the highest rates of cannabis dependence and greatest daily consumption. There might also be stable neuroanatomical differences between the groups. For example, we have recently reported that subjects with cocaine dependence who exhibit drug-induced psychosis display decreased white matter integrity (Willi et al. 2016a) and reduced subcortical regional gray matter volumes (Willi et al. 2016c) compared to non-psychotic subjects with cocaine dependence, despite similar total drug exposure. This may reflect a greater vulnerability to the neurotoxic effects of drugs, or possibly preexisting neurodevelopmental alterations, either of which could increase predisposition to psychosis. Similar differences could exist between cocaine- and methamphetamine-dependent groups in the present study, and future neuroimaging studies will be required to evaluate this possibility.

The addition of the cocaine + methamphetamine-dependent group to the study allowed us to examine the interesting question of how concurrent dependence would affect psychosis. Based on the present cohort, it is clear that being concurrently dependent on both drugs did not increase positive symptoms compared to cocaine dependence alone, and positive symptoms were lower than in methamphetamine-dependent subjects—an effect that approached statistical significance. The milder positive symptoms in the cocaine + methamphetamine-dependent group occurred despite this group having higher rates of HIV infection, significantly greater cocaine use, more alcohol dependence and a non-significantly greater use of heroin and cannabis than the methamphetamine-dependent group. It is possible that some of these differences could affect psychosis, although we have reported that greater opioid use in psychostimulant-dependent subjects is related to increased severity of negative symptoms only (Willi et al. 2016b). Rather, it seems most likely that the more severe positive symptoms in the methamphetamine-dependent group resulted from their significantly greater use of methamphetamine than the cocaine + methamphetamine group. Greater

combined use of the two drugs did not appear to have a synergistic effect on psychotic symptom severity.

The overall lack of cognitive differences in the present study is consistent with the finding that only positive symptoms differed between the groups: in schizophrenia spectrum disorders, neurocognitive performance is more strongly associated with negative or disorganized (Basso et al. 1998; O'Leary et al. 2000) but not positive symptoms, so it is perhaps not surprising that the groups performed equally on most neurocognitive measures. Indeed, cognition in the current combined cohort was correlated with the negative and disorganized factors, but not the other factors from the five-factor PANSS. Previous studies have noted that subjects with cocaine or methamphetamine dependence exhibit cognitive deficits in domains such as cognitive flexibility, but differences between the two groups are relatively minor when compared to healthy controls (Simon et al. 2002; van der Plas et al. 2009). Results from the urine drug screens indicated notable recent use of amphetamines, cocaine, cannabis, and opiates in the 48 h (longer for cannabis) prior to neurocognitive testing. While this might raise a note of caution in interpreting the neurocognitive data, we have previously reported in this cohort that with the exception of the effects of cannabis on the HVLT, a positive "hit" on the urine drug screen in the absence of signs of acute intoxication does not have a significant effect on cognitive scores (Waclawik 2016).

There are a number of limitations with the present study. First, most of the subjects were polysubstance users, and therefore, the groups do not represent "clean" samples of each type of drug dependence. This is typical of many marginalized urban populations (Cheng et al. 2016) and reflects the complex nature of comorbidity in this type of environment. For the most part, groups appeared to be evenly matched on most variables, and where differences occurred they were well documented and considered in the analysis. Second, recorded drug use in subjects as measured by the Time Line Follow Back questionnaire is not able to determine if subjects consumed cocaine or methamphetamine as part of a "binge," which could increase the severity of positive symptoms (Cheng et al. 2010; Kalayasiri et al. 2006b) compared to daily "chipping" consumption. Thus, it is possible that groups differed in their pattern of drug consumption, resulting in a differential liability to positive symptoms. Third, we compared the three groups across a considerable number of secondary variables (i.e., other than the primary outcome on the PANSS) which were not adjusted for multiple comparisons. These should therefore be considered in light of their descriptive and exploratory nature, and will require future replication. Our analysis of PANSS scores also only included age and route of drug administration as covariates, and not other variables where one or more groups differed, which reflected a balance between including variables that might influence positive symptoms against loss of statistical power. Fourth, in our study, subjects were categorized based on current rather than lifetime dependence, which may reduce the impact of previous forms of dependence on psychosis. However, current dependence was used for categorization as the literature largely indicates that current psychotic symptoms are much more likely to reflect more recent patterns of drug use (Harro 2015), versus drugs used multiple years previously. It should be noted, though, that multiple previous studies have noted that early cannabis exposure (by age 15) is associated with increased risk for both primary psychosis and cocaine-induced paranoia (Caspi et al. 2005; Kalayasiri et al. 2010). Finally, the current study is not able to assess whether groups differed in early development, as prenatal and childhood adversity significantly increases risk for psychosis (Trotta et al. 2015). Evaluation of such factors was beyond the scope of this study, but may represent an opportunity for future neuroimaging studies of neurodevelopmental markers.

In conclusion, there have been a number of previous studies that have compared psychosis in cocaine and methamphetamine users, which have focused on the presence of psychosis in an "all or nothing" manner or on specific symptoms. The present study is the first to compare symptom severity between these groups, and this approach identified an important increase in positive symptom severity in methamphetamine-dependent subjects. This effect appears specific to positive symptoms and is not likely to represent a general neurotoxic effect on the brain, as cognition did not differ between groups. This finding suggests that methamphetamine-dependent individuals may benefit in the future from access to mental health programs that include specific support for positive psychotic symptoms.

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Compliance with ethical standards 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 and received a modest honorarium for their time.

Conflicts of interest Drs. Smith, Thornton, Panenka, Vila-Rodriguez, Leonova, Lang and MacEwan report no competing interests. Mr(s). Alexander, Gicas, Willi, Kim, Boyeva, and Jones report no competing interests.

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