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The profile of psychiatric symptoms exacerbated by methamphetamine use

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ABSTRACT

Background: Methamphetamine use can produce symptoms almost indistinguishable from schizophrenia. Distinguishing between the two conditions has been hampered by the lack of a validated symptom profile for methamphetamine-induced psychiatric symptoms. We use data from a longitudinal cohort study to examine the profile of psychiatric symptoms that are acutely exacerbated by methamphetamine use.

Methods: 164 methamphetamine users, who did not meet DSM-IV criteria for a lifetime primary psychotic disorder, were followed monthly for one year to assess the relationship between days of methamphetamine use and symptom severity on the 24-item Brief Psychiatric Rating Scale. Exacerbation of psychiatric symptoms with methamphetamine use was quantified using random coefficient models. The dimensions of symptom exacerbation were examined using principal axis factoring and a latent profile analysis.

Results: Symptoms exacerbated by methamphetamine loaded on three factors: positive psychotic symptoms (suspiciousness, unusual thought content, hallucinations, bizarre behavior); affective symptoms (depression, suicidality, guilt, hostility, somatic concern, self-neglect); and psychomotor symptoms (tension, excitement, distractibility, motor hyperactivity). Methamphetamine use did not significantly increase negative symptoms. Vulnerability to positive psychotic and affective symptom exacerbation was shared by 28% of participants, and this vulnerability aligned with a past year DSM-IV diagnosis of substance-induced psychosis (38% vs. 22%, $\chi^2_{(df1)} = 3.66$, $p = 0.056$).

Conclusion: Methamphetamine use produced a symptom profile comprised of positive psychotic and affective symptoms, which aligned with a diagnosis of substance-induced psychosis, with no evidence of a negative syndrome.

1. Introduction

Methamphetamine and amphetamine (hereafter referred to collectively as methamphetamine) can produce a transient psychosis almost indistinguishable from acute paranoid schizophrenia (Angrist et al., 1974; Angrist and Gershon, 1970; Connell, 1966; McKetin et al., 2013). Differentiating between the two conditions with the existing diagnostic criteria is difficult based on presenting symptoms, resulting in misdiagnosis, suboptimal follow-up with a potentially poorer prognosis (Mathias et al., 2008). Given

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that around 30% of people diagnosed with methamphetamine-induced psychosis will be re-diagnosed with a schizophrenia spectrum disorder within 8 years (Niemi-Pynttari et al., 2013), reliable and validated symptom assessments are critical to minimizing initial errors and identifying whether transition to a primary psychotic disorder occurs. However, a validated symptom profile for methamphetamine-induced psychiatric symptoms is currently lacking.

A diagnosis of methamphetamine-induced psychosis is based on the DSM 5 criteria for substance-induced psychosis, which stipulates the presence of either delusions and/or hallucinations (American Psychiatric Association, 2013). Consistent with these criteria, most studies have noted the prominence of hallucinations and delusions, which are usually persecutory in nature (Akiyama, 2006; Angrist et al., 1974; Angrist and Gershon, 1970; Chen et al., 2003; Connell, 1966; Dore and Sweeting, 2006; Harris and Batki, 2000; Iwanami et al., 1994; Janowsky and Risch, 1979; Mahoney et al., 2008; Medhus et al., 2013; Srisurapanont et al., 2003). However, they fail to distinguish between methamphetamine-induced psychosis and schizophrenia on the remaining symptoms of schizophrenia (Hides et al., 2015; Medhus et al., 2013; Srisurapanont et al., 2003, 2011): disorganized speech (e.g., frequent derailment or incoherence), grossly disorganized or catatonic behavior, and negative symptoms (e.g., diminished emotional expression or avolition; American Psychiatric Association, 2013). Many studies report affective symptoms in methamphetamine-induced psychosis, including depressed mood (Akiyama, 2006; Hides et al., 2015; Iwanami et al., 1994), suicidal ideation (Akiyama, 2006), mania (Hides et al., 2015) and hostility (Akiyama et al., 2011; McKetin et al., 2008), but it is not clear whether these are core symptoms in methamphetamine psychosis or contemporaneous phenomena. Srisurapanont et al. (2011) found evidence of a positive syndrome (delusions, hallucinations and incoherent speech), a negative syndrome (poverty of speech, psychomotor retardation and flattened/incongruous affect) and an anxiety/depression syndrome (Srisurapanont et al., 2011), similar to that seen in people diagnosed with schizophrenia (Srisurapanont et al., 2011).

A key challenge is disentangling psychiatric symptoms caused by methamphetamine from those due to pre-existing psychiatric disorders (Mathias et al., 2008). Up to half of regular methamphetamine users have a comorbid psychiatric disorder, including 40% with major depression and 20% with a primary psychotic disorder (Glasner-Edwards et al., 2008; Hides et al., 2015; McKetin et al., 2011). Symptoms from these disorders can conflate the psychiatric symptom profile seen in people who use methamphetamine, making it difficult to identify diagnostic boundaries when making cross-sectional comparisons of symptom profiles. Excluding people with primary disorders does not fully address this problem because of the difficulty distinguishing between primary and substance-induced conditions (Mathias et al., 2008), and because participants may experience some pre-existing symptoms without fully meeting criteria for a primary disorder.

An alternative way to document what symptoms are induced by methamphetamine use is to examine which symptoms show a dose-related exacerbation during periods of methamphetamine use. Accordingly, we tracked the temporal concordance between level of methamphetamine use and psychiatric symptom severity in a longitudinal cohort of methamphetamine users who did not meet diagnostic criteria for a primary psychotic disorder. First, we examined the extent to which 24 psychiatric symptoms were exacerbated in a dose-related way with increasing methamphetamine use (with days of use as an indicator of methamphetamine dose). We then examined the factor structure of this symptom exacerbation to see whether it aligned with previously conceived notions of a positive syndrome, a negative syndrome and an anxiety/depressive syndrome. Finally, we used a latent profile analysis to see whether vulnerability to the identified symptom syndromes occurred in the same people, as would be expected if they reflected an underlying disorder. We also examined this latent symptom profile against a diagnosis of methamphetamine psychosis made using the Psychiatric Research Interview for DSM-IV Substance and Mental Disorders (PRISM-IV).

2. Method

2.1. Participants and procedure

Participants ($N = 164$) were methamphetamine users from the community who did not meet DSM-IV criteria for a lifetime primary psychotic disorder, assessed using the PRISM-IV Version 6 (Hasin et al., 1996). They were volunteers who self-identified as regular (monthly) methamphetamine users who were recruited through needle and syringe programs, word of mouth, and advertisements in magazines from Brisbane ($n = 92$), Melbourne ($n = 49$) and Sydney ($n = 23$), Australia (Hides et al., 2015). We excluded 24 participants who had a lifetime primary psychotic disorder, 7 who were not followed up, 4 who did not report methamphetamine use at follow-up, and 2 who had missing data on covariates. Participants provided informed consent prior to participation and they were reimbursed up to $30 AUD per interview; they were at least 18 years old, understood English and were willing to participate in follow-up interviews. The study received approval from the Griffith University Human Research Ethics Committee and this approval was ratified by other participating institutions.

At baseline, a face-to-face interview obtained psychiatric diagnoses, demographics, psychiatric and drug use history. Follow-up assessments of substance use and psychiatric symptom severity in the past month were undertaken monthly for one year (11 follow-ups in total). Follow-up interviews were conducted face-to-face at a mutually convenient location (e.g., at local health centres, cafes) or by phone where face-to-face interviews were not practical. Interviewers were psychology graduates who were trained in the interview protocol.

Participants completed a median of 11 follow-ups (range 1–11), with the majority of participants completing either 10 (22%) or all 11 follow-ups (57%). Psychiatric assessment data were complete for 78% of participants at follow-up (7–18% per follow-up were missing). There was no significant relationship between loss to follow-up and average days of methamphetamine use across the follow-up period ($r_s = 0.0002$, $p = 0.9918$), meeting the maximum likelihood estimate assumption of data that were missing at random.

2.2. Measures

2.2.1. Diagnoses. DSM-IV diagnoses were made using the PRISM-IV (Hasin et al., 1996), the best instrument currently available to reliably differentiate between substance-induced and other psychotic disorders (kappa 0.70–0.83; Torrens et al., 2004). The researchers were trained in the use of the PRISM by LH, an accredited user. Episodes of major depression and mania were identified using the Mini International Neuropsychiatric Interview Version 5.0.0 (Lecrubier et al., 1997), which has good validity against structured clinical interviews (kappas of 0.84 and 0.73, respectively; Sheehan et al., 1997).

2.2.2. Substance use. Days of methamphetamine use and other substance use in the past month were assessed using the Time-Line Follow-Back (TLFB). The TLFB is a validated measure of substance use (Fals-Stewart et al., 2000), which has 88% sensitivity, 96% specificity, a 95% hit-rate and 0.77 test-retest agreement for the use of amphetamines in the past 30 days (Fals-Stewart et al., 2000).

Other substance use was coded as: (1) cannabis use (0, 1–15, 16+ days); (2) alcohol use (0, 1–15, 16+ days); (3) other stimulant use in the past month; (4) antidepressant use in the past month; and, (5) benzodiazepine use in the past month.

2.2.3. Psychiatric symptom severity. The Brief Psychiatric Rating Scale (BPRS; Lukoff et al., 1986) was used to assess the severity of 24 psychiatric symptoms during the past month on a scale of 1 (not present) to 7 (extremely severe; Lukoff et al., 1986). The BPRS yields inter-rater reliability of 0.83 (Ventura et al., 1993) and this was 0.97 for the total BPRS score in the larger cohort from which this sample was drawn (Hides et al., 2015).

2.2.4. Other measures. Psychiatric history was assessed with the Interview for the Retrospective Assessment of the Onset and Course of Schizophrenia and Other Psychoses (Hafner et al., 1992). Age of onset for alcohol and other drug use was collected from the PRISM. Demographics included age, gender, education, marital status, immigrant status, ethnicity and employment.

2.3. Analysis

Data were analyzed using Stata SE version 12.1 (Stata Corporation, 2014). All tests were two-sided with significance set at $p < .05$. Group comparisons were made using a Pearson's Chi Square test for categorical measures and *t*-tests for continuous measures. Spearman rank correlations were used.

The relationship between methamphetamine use and psychiatric symptom severity was examined using random intercept regression models, with the time-varying BPRS item score for each month as the outcome variable and the time-varying number of methamphetamine-use days for each month as the predictor variable. We then included a random coefficient term for days of methamphetamine use in each model, from which we derived beta coefficients for each individual reflecting their change in BPRS item scores against days of methamphetamine use. These models adjusted for other substance use and also for time-invariant risk factors for psychosis (age, sex, immigrant status, family history of a primary psychotic disorder; McGrath, 2007). A Hausman test was used to confirm that there was no significant difference between the within-subject and between-subject effects for days of methamphetamine use. As BPRS item scores reflected a Poisson distribution, a Poisson regression model was estimated with a log link function, an unstructured correlation matrix, and a random intercept to allow for heterogeneity in BPRS item scores between individuals.

Principal axis factor analysis with an oblique (oblimin) rotation was used to explore the factor structure of the beta coefficients derived from the above models. Latent profile analysis, in MPlus v7.2, was applied to the factor scores to derive substantively meaningful groups of people that were similar in their pattern of symptom exacerbation (Hagenaars and McCutcheon, 2002; Lazarsfeld and Henry, 1968; Muthén, 2004). Nested models were compared to determine the number of classes that provided the best model fit. The fit of models was compared by the bootstrap of the Lo-Mendell-Rubin Likelihood Ratio Test (Lo et al., 2001), the Bayesian Information Criterion (BIC; Yang, 2006) and entropy. Class membership was decided based on the (maximum) probability of membership in each class.

3. Results

3.1. Characteristics of the sample

Participants had a mean (SD) age of 32.3 (8.2) years, 60% were male, all were from an English-speaking background, the majority were Caucasian (85%) and born in Australia (91%). Most were single, separated or divorced (74%); 38% had a trade certificate and 9% held a university degree. Forty six per cent had a lifetime DSM-IV substance-induced psychosis (62% within the past year), 21% had a family history of a psychotic disorder, and 12% had ever been hospitalized for a psychiatric problem.

The mean (SD) age of first methamphetamine use of was 19.7 (6.4) years and 88% had injected the drug. Participants had used methamphetamine on a mean (SD) of 10 (9) days in the past month at baseline. Methamphetamine use occurred during 80% of follow-up months, on a mean (SD) of 8 (8) days each month. Other drug use consisted primarily of cannabis (70% of months; mean (SD) of 18 (12) days) and alcohol (71% of months; mean (SD) of 12 (10) days), with other drug use being less common: 18% of months for benzodiazepines, 15% for heroin, 16% for ecstasy and 5% for cocaine.

Months where antipsychotic medication and/or antidepressant medication were taken were excluded from the analysis to discount the acute effects of these drugs on BPRS symptom severity (217 months in total: 41 for antipsychotic medication, 165 for antidepressants and 11 for both). This left a total of 1370 months of data for the analysis for the combined sample.

3.2. The relationship between methamphetamine use and BPRS item severity

Mean BPRS item scores over the follow-up period were low (range 1.0–2.6, for details see Fig. 1 in the Supplementary Material). Greater days of methamphetamine use were associated with more severe hallucinations, tension, motor hyperactivity, hostility, suspiciousness, distractibility, bizarre behavior, unusual thoughts, anxiety, excitement, suicidality, guilt, depression, somatic concern and self-neglect (Fig. 1). There was no significant relationship between days of methamphetamine use and the severity of remaining symptoms ($p > 0.05$, for details see Table S1).

3.3. Factor analysis of methamphetamine-related symptom exacerbation

Beta coefficients for each individual reflecting their symptom exacerbation (increase in BPRS item scores with increasing days of methamphetamine use) were included in a principal factor analysis, which revealed three factors with eigenvalues >1, explaining 91% of the variance (for details see Table S2). An oblique rotation indicated three factors (Table 1) corresponding to (1) an affective syndrome dominated by depression, suicidality, hostility and self-neglect (Factor 1); (2) positive psychotic symptoms of suspiciousness, unusual thought content and hallucinations (Factor 2); and, (3) symptoms reflecting the psychomotor effects of methamphetamine: motor hyperactivity, excitement, distractibility and tension (Factor 3). Factors 1 and 2 were highly correlated ($r_s = 0.61$, $p < 0.001$) and neither were associated with Factor 3 ($r_s < 0.05$). Guilt loaded on both Factors 1 and 2, bizarre behavior loaded on Factors 2 and 3, and tension loaded on Factors 1 and 3. However, most items clearly delineated their parent latent factor. As the size and extent of cross-loading was minimal, the three cross-loading items were retained, and factor scores were estimated post-rotation.

3.4. Latent profile analysis of symptom exacerbation

Latent profile analysis was applied to the factor scores derived from the factor analysis. A two-class model significantly improved model fit over a single-class model (LRT = 128.1, $p < 0.001$, BIC = 1040; entropy = 0.68). Fit was further improved by the three-class model (LRT = 55.2, $p < 0.001$, BIC = 1034; entropy = 0.81), but not by the inclusion of a fourth class (LRT = 41.6, $p = .162$, BIC = 1045;

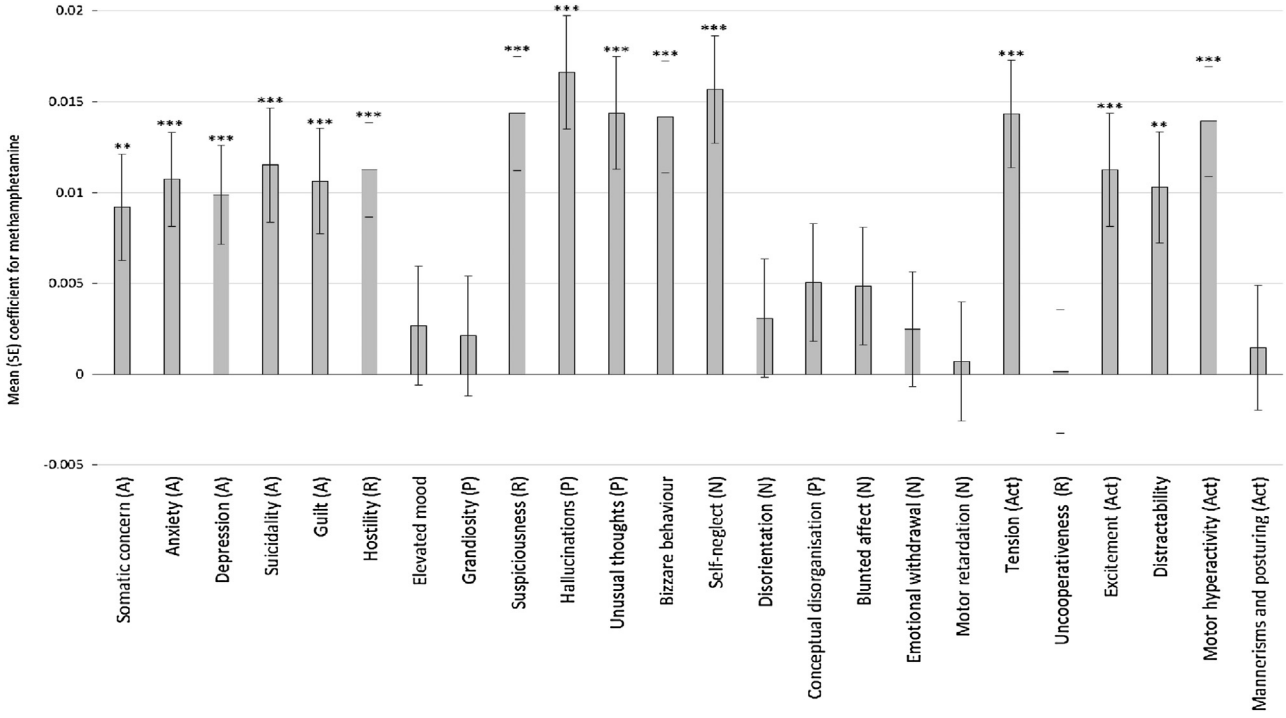

Fig. 1. Mean (SE) coefficient for methamphetamine use on each BPRS item (adjusted for other substance use) reflecting the change in BPRS item symptom severity with days of methamphetamine use.

Table 1
Item loadings of three factors extracted from principal axis factoring with an oblique oblimin rotation.

BPRS item	Factor 1 "Affective symptoms"	Factor 2 "Positive psychotic symptoms"	Factor 3 "Stimulant effects"	Uniqueness
Somatic concern	0.42			0.78
Anxiety	0.47			0.69
Depression	0.71			0.29
Suicidality	0.70			0.56
Guilt	0.45	0.34		0.52
Hostility	0.67			0.56
Suspiciousness		0.88		0.19
Hallucinations		0.67		0.57
Unusual thought content		0.89		0.22
Bizarre behavior		0.41	0.37	0.53
Self-neglect	0.61			0.64
Tension	0.32		0.43	0.65
Excitement			0.75	0.45
Distractibility			0.61	0.57
Motor hyperactivity			0.90	0.19

Note: Only factor loadings > .30 are shown.

entropy = 0.80). We therefore chose the three-class model as best fitting.

Symptom cluster profiles for the three classes are displayed in Fig. 2. Half the participants were reflected by the profile of Class 1, which had relatively low symptom exacerbation on all three symptom clusters. Class 2 participants (28%) reported greater symptom exacerbation of both the affective and the psychotic symptom clusters, while Class 3 participants (22%) were comparatively more vulnerable to the psychomotor symptom cluster. The mean coefficients for each BPRS item (reflecting the severity of symptom exacerbation), and mean factor scores, for each class are provided in Table S3.

Participants who were more vulnerable to psychotic and affective symptom exacerbation (Class 2) showed a trend toward a higher past-year prevalence of substance-induced psychosis (38%) compared to participants in Classes 1 and 3 (22% each, $\chi^2_{(df1)} = 3.66$, $p = 0.056$). Class 2 and 3 had greater average days of methamphetamine use over the study period than Class 1. There were no significant group differences in other variables measured (see Table S4).

4. Discussion

We found that methamphetamine use increased the severity of a range of psychiatric symptoms. Specifically, the number of days of methamphetamine use within a given month increased the severity of 15 BPRS item scores within that month. Symptoms exacerbated by methamphetamine use clustered on three dimensions: positive psychotic symptoms, affective symptoms and psychomotor agitation. There was no evidence that methamphetamine exacerbated other BPRS symptoms, including negative symptoms of psychosis. We also found evidence of a latent symptom profile that aligned with a diagnosis of methamphetamine psychosis, and that comprised both positive psychotic and affective symptoms.

These findings reinforce the DSM 5 substance-induced psychosis criteria of hallucinations and delusions (American

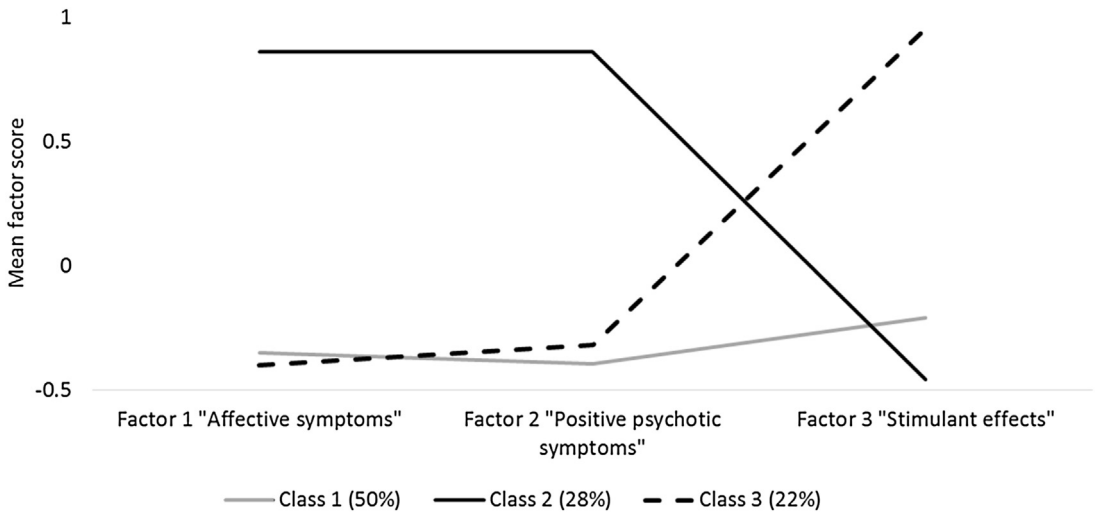

Fig. 2. A comparison of factor scores by class.

Psychiatric Association, 2013), and they are consistent with past research in showing that delusions in methamphetamine psychosis are primarily persecutory in nature (Akiyama, 2006; Chen et al., 2003; Dore and Sweeting, 2006; Harris and Batki, 2000; Iwanami et al., 1994; Srisurapanont et al., 2003). The affective accompaniment to this psychosis (dominated by depression, suicidality, hostility and self-neglect) is not recognized in the diagnostic criteria for substance-induced psychosis (American Psychiatric Association, 2013) but our results are consistent with Srisurapanont et al. (2011), who also found an affective symptom dimension, and other research showing elevated levels of depression among people diagnosed with methamphetamine psychosis relative to other users of the drug (Chen et al., 2003; Lecomte et al., 2013). These collective findings suggest that affective symptoms may be a core feature of the methamphetamine psychosis, perhaps similar to depression with psychotic features or schizoaffective disorder (Tsuang et al., 1982). Affective symptoms are also commonly seen in people with schizophrenia, including in the prodromal phase of first episode psychosis (Tandon et al., 2009), and can arise secondary to the distress caused by psychotic symptoms (Birchwood, 2003). Further research should elucidate whether the affective syndrome is more prominent in methamphetamine psychosis, or different in nature, than affective symptoms seen in other psychotic disorders.

We found no indication that methamphetamine use increased negative symptoms, suggesting that this may be a way of differentiating between methamphetamine-induced psychosis and schizophrenia. Although the absence of a negative syndrome is inconsistent with the findings of Srisurapanont et al. (2011), only 8% of patients in the Srisurapanont et al. study had reported negative symptoms. These symptoms may have been secondary to psychosis or heavy drug use (e.g., due to deprivation, intoxication, or the effects of antipsychotic medication (Tandon et al., 2009)) or the result of misdiagnosis (i.e., patients with schizophrenia being misdiagnosed as having methamphetamine psychosis). Because we only examined symptom exacerbation during periods of methamphetamine use, we cannot discount the possibility that negative symptoms may manifest subsequent to methamphetamine-induced psychosis as part of a residual symptom profile (Tandon et al., 2009).

The exacerbation of psychomotor symptoms (motor hyperactivity, excitement, distractibility and tension) by methamphetamine is typical of a stimulant drug. A different subgroup of people were vulnerable to psychomotor symptom exacerbation than were vulnerable to affective and positive psychotic symptoms. This may be related to different neural substrates underpinning the psychomotor and the psychogenic effects of methamphetamine (i.e., the nigrostriatal pathway and mesocorticlimbic pathways respectively; Hsieh et al., 2014); and it may suggest distinct neuropathological mechanisms underlying different symptom dimensions, not dissimilar to the emerging view that there are multiple and distinct etiological pathways underpinning different symptoms in psychotic disorders (McGrath et al., 2015; van Os, 2014; Zavos et al., 2014).

Our approach assumes that symptoms exacerbated in a dose-related manner during periods of methamphetamine use are due to the drug. This assumption is a pragmatic one and not intended to imply a direct causal relationship. We adjusted for patterns of concurrent substance use, and a range of risk factors for psychosis, to reduce the possibility that these factors might account for more severe psychiatric symptoms seen during periods of heavy methamphetamine use. However, unmeasured factors (e.g., concurrent stressors), particularly those that co-occur with heavy methamphetamine use, may have contributed to the symptom exacerbation. Although we rely on self-reported methamphetamine use, self-report has been found to be an accurate and reliable indicator of drug use (Darke, 1998), and our measure of days of methamphetamine use has had excellent agreement with relevant biomarkers in other research (Fals-Stewart et al., 2000).

In sum, these results highlight the potential for methamphetamine use to increase the severity of a range of psychiatric symptoms, and the need to distinguish these symptoms from underlying psychiatric disorders, to avoid misdiagnosis and suboptimal care. Whether these symptom clusters can be used to more accurately distinguish between methamphetamine-induced and primary psychotic disorders, as well as other psychiatric disorders, requires further research.

Contributors

All authors contributed to the writing and review of the manuscript.

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The funders of the study played no role in the design and conduct of the study; collection, management, analysis, interpretation of the data; or the preparation, review or approval of the manuscript.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugalcdep.2016.01.018.

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