The Profile and Structure of Psychotic Symptoms associated with Methamphetamine Use

Alexandra Voce

Thesis submitted for the degree of Doctor of Philosophy at
the Australian National University

2021

Abstract

Background: Methamphetamine use can precipitate a transient psychotic state, referred to as methamphetamine-associated psychosis (MAP). It can be challenging to distinguish MAP from schizophrenia (SZ) in clinical settings, as these disorders share a similar psychiatric symptom profile. The overlap between MAP and SZ has led some people to question whether MAP is better conceptualised as a distinct clinical entity, or as a precipitation of SZ. To address these issues, this thesis aimed to examine the profile and underlying structure of psychotic symptoms associated with methamphetamine use.

Methods: Four research approaches were adopted. A systematic review (study one) was conducted to canvas the existing literature for specific psychiatric symptoms, and the duration of symptoms, in MAP (k=94; n=7387). Univariate regression (study two) was used to investigate the association between methamphetamine use and psychiatric symptom prevalence in a cohort of people with primary psychosis (n=636). Exploratory factor analysis (study three) was used to investigate the factor structure of psychiatric symptoms among a cross-sectional survey of people who use methamphetamine (n=153). Latent class analysis (LCA) was used to examine profiles of lifetime psychotic symptoms among people currently using methamphetamine (n=554, study four), and the concordance between these profiles and a diagnosis of SZ was assessed. In study five, LCA was used to investigate profiles of current psychiatric symptoms among people with past-month methamphetamine use (n=160), and the alignment of these profiles with diagnoses of MAP and SZ was examined.

Results: The systematic review (study one) found that most commonly reported symptoms of MAP were persecutory delusions, auditory and visual hallucinations, hostility, and conceptual disorganisation. One-quarter of people with MAP reported persistent psychotic symptoms (>1 month after drug cessation). Methamphetamine use was associated with a

higher prevalence of hallucinations and persecutory delusions among people with SZ (study two). A three-factor model of psychiatric symptoms was identified amongst people who use methamphetamine (study three), including a positive/activation factor and an affective factor (both associated with methamphetamine use), and a negative symptoms factor (associated with depressant drug use, but not methamphetamine use). Follow-up LCA showed that negative symptoms were not observed among people with positive/activation symptoms. LCA revealed three profiles of lifetime psychotic symptoms (study four), and three profiles of current psychiatric symptoms (study five) amongst methamphetamine users. In both LCA models, a class of individuals who experienced persecutory delusions and hallucinations were differentiated from a smaller class who experienced a wider range of symptoms (i.e. non-persecutory delusions) and who were more likely to meet criteria for SZ.

Conclusions: Persecutory delusions, hallucinations, hostility, and conceptual disorganisation are prominent symptoms of MAP. Negative symptoms do not appear to be a component of MAP, but rather are associated with polysubstance use. Two distinct psychotic syndromes exist among people who use methamphetamine. These empirically-derived syndromes partially aligned with current diagnostic constructs, and are consistent with the need for a MAP diagnostic category separate from SZ. Greater consideration of specific symptoms (e.g., negative symptoms and non-persecutory delusions) may improve diagnostic accuracy by identifying people with a higher risk of SZ.

Table of Contents

Publications included in thesis

Publications in this thesis contain only original research. All authors who contributed to this work have been properly acknowledged, and the individual contributions of each author are outlined below. No author declares any conflict of interest.

Study One

Voce, A., McKetin, R., Calabria, B., Burns, R., & Castle D. (2019). A systematic review of the symptom profile and course of methamphetamine associated psychosis. *Substance Use and Misuse, 54*(4): 549-559.

Author	Contribution
Voce, A. (Candidate)	Generated research questions (35%), Designed search strategy (33%), Identified studies and extracted data (80%), Analysed data (60%), Wrote paper (80%)
McKetin, R.	Generated research questions (35%), Designed search strategy (33%), Identified studies and extracted data (20%), Analysed data (20%), Wrote paper (20%), Reviewed paper (25%)
Burns, R.	Generated research questions (10%), Reviewed paper (25%)
Castle, D.	Generated research questions (10%), Reviewed paper (25%)
Calabria, B.	Generated research questions (10%), Designed search strategy (33%), Analysed data (20%), Reviewed paper (25%)

Signed_____

Dr Richard Burns

Chair of Ph.D supervisory panel

Signed_____

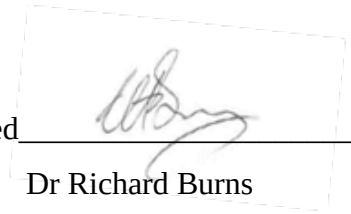
Alexandra Voce

Ph.D candidate

Study Two

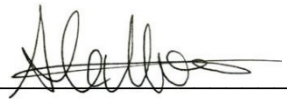
Voce, A., McKetin, R., Burns, R., Castle D., & Calabria, B. (2018). The relationship between illicit amphetamine use and psychiatric symptom profiles in schizophrenia and affective psychoses. *Psychiatry Research, 265*: 19-24.

Author	Contribution
Voce, A. (Candidate)	Generated research questions (40%), Designed analysis strategy (40%), Analysed data (70%), Wrote paper (90%)
McKetin, R.	Generated research questions (30%), Designed analysis strategy (30%), Analysed data (20%), Wrote paper (10%), Reviewed paper (25%)
Burns, R.	Generated research questions (5%), Analysed data (10%), Reviewed paper (25%)
Castle, D.	Generated research questions (20%), Designed analysis strategy (30%), Reviewed paper (25%)
Calabria, B.	Generated research questions (5%), Reviewed paper (25%)

Signed 

Dr Richard Burns

Chair of Ph.D supervisory panel

Signed 

Alexandra Voce

Ph.D candidate

Study Three

Voce, A., Burns, R., Castle D., Calabria, B., & McKetin, R. (2019). Is there a discrete negative symptom dimension in people who use methamphetamine? *Comprehensive Psychiatry, 93*: 27-32.

Author	Contribution
Voce, A. (Candidate)	Generated research questions (60%), Designed analysis strategy (35%), Analysed data (50%), Wrote paper (80%)
McKetin, R.	Generated research questions (20%), Designed analysis strategy (30%), Analysed data (25%), Wrote paper (20%), Reviewed paper (35%)
Burns, R.	Generated research questions (10%), Designed analysis strategy (30%), Analysed data (25%), Reviewed paper (25%)
Castle, D.	Generated research questions (5%), Reviewed paper (20%)
Calabria, B.	Generated research questions (5%), Reviewed paper (20%)

Signed_____

Dr Richard Burns

Chair of Ph.D supervisory panel

Signed_____

Alexandra Voce

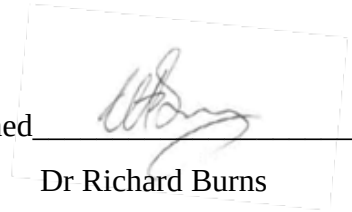
Ph.D candidate

Study Four

McKetin, R., Voce, A., Burns, R., Ali, R., Lubman, D., Baker, A., David, C. (2018). Latent psychotic symptom profiles amongst people who use methamphetamine: what do they tell us about existing diagnostic categories? *Frontiers in Psychiatry,* 9: 578.

Author	Contribution
Voce, A. (Candidate)	Generated research questions (30%), Designed analysis strategy (30%), Analysed data (40%), Wrote paper (20%)
McKetin, R.	Generated research questions (70%), Designed analysis strategy (70%), Analysed data (20%), Wrote paper (80%)

Burns, R.	Analysed data (40%), Reviewed paper (20%)
Castle, D.	Reviewed paper (20%)
Ali, R.	Reviewed paper (20%)
Lubman, D.	Reviewed paper (20%)
Baker, A.	Reviewed paper (20%)

Signed 

Dr Richard Burns

Chair of Ph.D supervisory panel

Signed 

Alexandra Voce

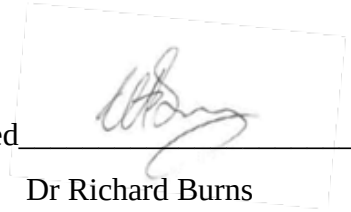
Ph.D candidate

Study Five

Voce, A., Burns, R., Castle D., Calabria, B., & McKetin, R. (2021). A latent class analysis of current psychiatric symptom profiles associated with past-month methamphetamine use. *Psychiatry Research, 298,* 113760.

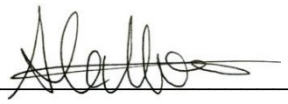
Author	Contribution
Voce, A. (Candidate)	Generated research questions (35%), Designed analysis strategy (30%), Analysed data (70%), Wrote paper (100%)
McKetin, R.	Generated research questions (20%), Designed analysis strategy (20%), Analysed data (20%), Reviewed paper (25%)
Burns, R.	Generated research questions (15%), Designed analysis strategy (20%), Analysed data (10%), Reviewed paper (25%)

Castle, D.	Generated research questions (15%), Designed analysis strategy (15%), Reviewed paper (25%)
Calabria, B.	Generated research questions (15%), Designed analysis strategy (15%), Reviewed paper (25%)

Signed 

Dr Richard Burns

Chair of Ph.D supervisory panel

Signed 

Alexandra Voce

Ph.D candidate

Other research output during candidature

Peer-reviewed publications

McKetin, R., Voce, A., Burns, R., & Quinn, B. The Short Barriers Questionnaire (SBQ): validity, factor structure and correlates in an out-of-treatment sample of people dependent on methamphetamine. *Journal of Substance Abuse Treatment, 116,* 108029

Voce, A., & Anderson, K. (2019). The interaction between parental behavior and motivations to drink alcohol in high school students. *Am J Drug Alcohol Abuse*: 1-9.

McKetin, R., Baker, A., Dawe, S., Voce, A., & Lubman, D. (2017). Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Research, 25*1: 349–354.

McKetin, R., Voce, A., Burns, R., & Shanahan, M. (2017). Health-related quality of life among people who use methamphetamine. *Drug and Alcohol Review*, *38*(5):503-509.

McKetin, R., Gardner, J., Baker, A. L., Dawe, S., Ali, R., Voce, A., Leach, L. S., & Lubman, D. I. (2016). Correlates of transient versus persistent psychotic symptoms among dependent methamphetamine users. *Psychiatry Research, 30*(238): 166-71.

McKetin, R., Dawe, S., Burns, R., Hides, L., Kavanagh, D., Teesson, M., Young, R., Voce, A., & Saunders, J. (2016). The profile of psychiatric symptoms exacerbated by methamphetamine use. *Drug Alcohol Dependence, 1*(161):104-9.

Other publications

McKetin, R., Voce, A., & Burns, R. (2017). *Research into methamphetamine use in the ACT.* ACT Health, Department of Health, Australian Government. Canberra, Australia.

Conference presentations

Voce, A., & McKetin, R. (2017, November). *Methamphetamine Use in the ACT.* Drug Services Forum by ACT Health, 2017.

Voce, A., McKetin, R., Calabria, B., Burns, R., & Castle, D. (2017, October). *The symptom profile of methamphetamine-induced psychosis: A systematic review*. International Federation of Psychiatric Epidemiology Congress, 2017.

Voce, A., McKetin, R., Burns, R., Castle, D., & Calabria, B. (2017, October). *The relationship between amphetamine use and psychotic symptoms in those with primary psychotic disorders*. International Federation of Psychiatric Epidemiology Congress, 2017.

Voce, A., McKetin, R., Burns, R., Castle, D., & Calabria, B. (2017, June). *The association between amphetamine use and psychotic symptoms in those with schizophrenia versus affective psychoses*. Australian Society of Medical Research New Investigator Forum, 2017.

Voce, A., McKetin, R., Calabria, B., Burns, R., & Castle, D. (2017, February). *The symptom profile and clinical course of methamphetamine-induced psychosis: A systematic review*. Iceman Cometh: Drugs, Alcohol and Mental Health Conference, University of Melbourne, 2017.

Voce, A., McKetin, R., Calabria, B., Burns, R., & Castle, D. (2016, November). *The symptom profile of methamphetamine-induced psychosis: A systematic review*. Australasian Professional Society on Alcohol and Other Drugs Conference, 2016.

McKetin, R., Dawe, S., Burns, R. A., Hides, L., Kavanagh, D., Teesson, M., Young, R., Voce, A., & Saunders, J. (2016, November). *Correlates of transient versus persistent psychotic symptoms among dependent methamphetamine users*. Poster Highlights Plenary session in the Australasian Professional Society on Alcohol and Other Drugs Conference, 2016.

Acknowledgements

I gratefully acknowledge the funding received towards my doctorate from the Australia Postgraduate Scholarship program. This scholarship allowed me to devote my full attention and time to this research. I wish to express my sincerest gratitude to my supervisor, Associate Professor Rebecca McKetin, for her consistent support and patience throughout this entire process, and for imparting her immense knowledge in the field. Thank you to my chair Dr Richard Burns, and my co-supervisors Professor David Castle and Dr Bianca Calabria, for their continual encouragement and guidance, I always left our panel meetings with a restored sense of confidence and motivation. I wish to express my gratitude to the SHIP advisory committee, particularly Professor Vera Morgan, for allowing me access to the SHIP dataset. I wish to acknowledge the support and input of the ACT project advisory group coordinated by ACT Alcohol, Tobacco and Other Drug (ATODA), including James Bint, Helene Delany, Carrie Fowlie, Chris Gough, David McDonald, and Julie Robert. I am incredibly grateful to the individuals who participated in my research for their trust and time.

On a personal level, I want to thank my Dad and Stepmum, Stephen and Ginny, my twin sister Isabella, and my friends (particularly Lorien, Alinta, Topher, and Purcel) for helping me to keep things in perspective and for lifting me up in times of stress. I want to thank my wonderful partner, Brendan, for constantly supporting and inspiring me. I am proud that we have shared this entire journey together. I love you.

Finally, a special thank you to my mother, Louise, for everything she has done for me. Mum, you have made everything that I have ever achieved possible.

List of Tables in Introduction

List of Figures in Introduction

List of Abbreviations

ACT	Australian Capital Territory
APA	American Psychiatric Association
BPRS	Brief Psychiatric Rating Scale
CI	Confidence interval
CIDI	Composite International Diagnostic Interview
DSM	Diagnostic and Statistical Manual of Mental Disorders
EFA	Exploratory factor analysis
ICD	International Classification of Disease
LCA	Latent class analysis
MAP	Methamphetamine-associated psychosis
OR	Odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SD	Standard deviation

SZ	Schizophrenia
UK	United Kingdom
UN	United Nations
USA	United States of America

Thesis Introduction

Part A: Methamphetamine use

Overview

Methamphetamine – and its less potent chemical analogue amphetamine (henceforward collectively referred to as methamphetamine) – are categorised in a class of drugs referred to as amphetamine-type stimulants (1). These synthetic psychostimulants act on the central nervous system by increasing levels of dopamine, serotonin, and noradrenaline producing, *inter alia*, feelings of euphoria, confidence, energy, and increased attention (2-4). In 2016, it was estimated that approximately 1.4% of the Australian adult population had used illicit methamphetamine in the past 12 months (5). The most commonly used form of the drug in Australia is crystalline methamphetamine, which is typically smoked or injected. Most people who use methamphetamine do so infrequently and without developing dependence (colloquially termed addiction); however, a substantial minority ultimately transition to frequent and dependent use (6). Somewhat hidden due to drug criminalisation, these people often form a highly disadvantaged and marginalised population with high levels of polysubstance use and complex psychiatric comorbidity (7, 8).

History of Methamphetamine Use

The first-documented widespread use of methamphetamine occurred during World War II, when the drug was used by soldiers to reduce hunger and fatigue (9, 10). Between the 1930s and 1960s, methamphetamine-based pharmaceuticals (under brand names such as Benzedrine and Methedrine) were liberally prescribed for various health complaints, including migraines, excessive body fat, poor concentration, narcolepsy, anxiety, depression, and schizophrenia (9, 11). With wider therapeutic use of methamphetamine, awareness of the

potential for physical and psychological dependence and associated harms of the drug increased (12). To curb the problematic use of these drugs, the United Nations signed the Convention on Psychotropic Substances treaty in 1971, placing a regulatory framework around the supply of psychostimulants and other psychoactive drugs (1). Methamphetamine is currently listed as Schedule 8 controlled substance in Australia; a classification for drugs that have legitimate medical use but are also considered to have a high risk of abuse and dependence (1). In Australia, low-dose methamphetamines are approved as oral prescription medications (i.e. dexamphetamine) for the treatment of conditions such as attention-deficit hyperactivity disorder and narcolepsy (13); however, it is illegal to possess, manufacture, supply, or distribute methamphetamines without governmental authorisation.

Forms and administration of methamphetamine

In Australia, methamphetamine is sold on the illicit drug market in three main physical forms: a powder (referred to as "speed"), a concentrated paste or liquid ("base"), and a refined crystalline form ("ice") which is the most common form used in Australia (5, 6). Routes of administration vary depending on the form of the drug and include swallowing (all forms), snorting (powdered and crystal methamphetamine), smoking (crystal methamphetamine), or injection (all forms). According to the Australian National Drug Strategy Household Survey, smoking is the most common route of administration for past-year users of crystal methamphetamine in Australia (68%), followed by injection (19%) (5). Intravenous injection provides the most immediate and intense effects (14), however, a similarly intense and rapid effect can be achieved by smoking or inhaling crystal methamphetamine (15).

Acute Effects of Methamphetamine

The half-life of methamphetamine in humans is approximately 11 hours, and the subjective effects of the drug typically last 4 – 8 hours, with residual effects persisting for up to 12 hours (2). Methamphetamine stimulates the central nervous system, increasing heart rate, blood pressure, and body temperature. The subjective effects include a "rush" of euphoria, alertness, and energy, in conjunction with an increased sense of well-being, increased sex drive, reduced appetite, behavioural disinhibition, and reduced need for sleep (3, 4, 10). Acute intoxication can also induce symptoms of psychiatric disturbance, including hallucinations, delusions, hostility, and symptoms of anxiety (including panic).

Extent of Use

In 2019, it was estimated that 29 million people globally had used illicit methamphetamine in the previous 12 months, making methamphetamine the second most commonly used class of illicit drugs worldwide after cannabis (14). Methamphetamine use is particularly common in Asia, North America, and Australia. In 2016, the Australian National Drug Strategy Household Survey estimated that approximately 6.3% of the general population (1.3 million people) aged over 14 years had used illicit methamphetamine in their lifetime (5), and approximately 1.4% (340 000 people) had used the drug in the previous 12 months. Of those who had used methamphetamine in the previous year, most had used the drug less than once per month (69%), 11% had used once per month, and 20% used the drug on a weekly or daily basis. Thus, most people who use methamphetamine in their lifetime will use on an infrequent basis (16), often as a recreational party drug, appetite suppressant, to aid work or study performance, or as a coping strategy to alleviate negative emotions. However, regular methamphetamine use is associated with a risk of developing dependence (17).

Dependence on Methamphetamine

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) 4th Edition (166), substance dependence is characterised by withdrawal symptoms following acute intoxication, psychological preoccupation with the drug, and tolerance in which increasingly higher doses are required to achieve the same level of initial effect (18). It has long been recognised that the pharmacological symptoms of tolerance and withdrawal occur in the context of behavioural and cognitive symptoms that characterise substance-related problems. In the DSM-5, these symptoms are described in three clusters involving impairments in control over substance use (i.e. cravings, inability to reduce use), impairments in social functioning (i.e. failure to fulfil obligations, interpersonal problems due to use), and engagement in risky substance use (i.e. continued use despite detriments to physical or psychological health). Methamphetamine dependence has been subsumed in the DSM-5 under the diagnosis of a methamphetamine use disorder (18). Symptoms of methamphetamine withdrawal can last up to two weeks after intoxication (6) and can include fatigue, lethargy, appetite disturbances, anxiety, hostility, psychomotor retardation, poor concentration, and strong cravings for the drug (15). Depressive symptoms are particularly common in methamphetamine withdrawal and include feelings of hopelessness, social withdrawal, anhedonia, or suicidal ideation (19).

Among people who infrequently use methamphetamine, approximately one in five will transition to regular dependent use (6). In 2013-2014, Degenhardt and colleagues (20) estimated that 268 000 Australians aged 15-54 years were dependent on the drug. Dependence is more likely with injection or smoking compared to other routes of administration (17, 21). Due to high purity levels and ease of administration through smoking, people who use crystal methamphetamine are nearly twice as likely to develop dependence compared to those who use other forms of the drug (17). Individuals who are dependent on illicit substances are unable to discontinue use despite negative impacts on their

interpersonal relationships, employment, and/or physical and psychological health (18). These individuals are more likely than the general population to experience family breakdown, physical and sexual assault, domestic violence, social isolation and marginalisation, unemployment, homelessness and legal and financial difficulties. Compared to the general population, people who are dependent on methamphetamine are also more likely to experience a range of psychiatric disorders, notably major depression, generalised anxiety disorder, and post-traumatic stress disorder (22).

Polysubstance Use

Most people who use methamphetamine will also use a range of other licit and illicit substances, primarily tobacco, cannabis, alcohol, and heroin (8). These substances are often used simultaneously or concurrently with methamphetamine, in part, to reduce methamphetamine-related arousal and anxiety or to ease withdrawal symptoms (23, 24). Some people frequently engage in heavy use of both methamphetamine and heroin, shifting between these drugs depending on whichever is available and affordable at the time (23). The use of multiple substances is referred to as polysubstance use, and this pattern can increase the toxicity associated with methamphetamine use (25) and can compound negative consequences on an individual's physical and mental health (23).

Part B: Methamphetamine-associated psychosis (MAP)

One of the most widely-documented outcomes of methamphetamine use is the capacity for the drug to precipitate a transient psychosis, even among people without a pre-existing psychotic disorder (26). This acute psychotic syndrome, hereafter referred to as methamphetamine-associated psychosis (MAP), has a lifetime prevalence of 43% in people with methamphetamine use disorders (27). The MAP syndrome is characterised by the

presence of delusions or hallucinations (18), referred to as positive psychotic symptoms (Table 1), which typically resolve within two or three weeks after drug cessation (28).

Table 1. Description of Positive Psychotic Symptoms

Symptom	DSM-5 definition	Commonly described types:
Delusions	A false belief based on an incorrect inference about external reality that is firmly held, despite what almost everyone else believes, and despite what constitutes incontrovertible and obvious proof or evidence to the contrary.	*Persecution* (belief that one is being attacked or conspired against), *reference* (belief that events or features in the environment have a particular significance to oneself), *grandiosity* (belief of inflated worth, power, knowledge, or connection to a deity or famous person), *control* (belief that feelings, thoughts, or actions are being controlled by external forces), *thought broadcasting* (belief that one's thoughts are being broadcast out loud for others to perceive).
Hallucinations	A perception-like experience with the clarity and impact of a true perception, but without the external stimulation of the relevant sensory organ.	*Visual* (sight – often involve seeing visions of people or shadows), *auditory* (sound – often involve hearing voices), *tactile* (touch), *gustatory* (taste), *olfactory* (smell).

However, there are substantial variations in the profile and duration of symptoms reported among people with MAP.

Symptom Profile of MAP

Early research into the MAP syndrome as identified delusions and hallucinations as core components of the symptom profile, which are often accompanied by affective symptoms (anxiety, depression, and hostility) – and to a lesser extent – disorganised

psychotic symptoms (defined as fragmentations in logical and goal-directed capacities for speech, thought, affect, or movement). The first cases of MAP were described by Young and Scoville in 1938 and several subsequent analogous case reports over the following two decades (29-33). In these cases, people taking amphetamine-based pharmaceuticals exhibited prominent delusions of persecution and reference, verbal hallucinations, and distressing visions. The reports described talkativeness, excessive psychomotor activity, and distractibility, and in some cases, fragmented and circumstantial speech. The first extensive study of MAP was published in a pioneering monograph by Phillip Connell in 1958 (34), which described the symptom profile of 42 patients with MAP. Paranoia was a central feature, occurring with full awareness and orientation, and often in combination with auditory and visual hallucinations, ideas of reference, and anxiety. This profile was replicated in a handful of laboratory experiments conducted during the 1970s and 1980s, in which people who used illicit drugs (many without a history of psychosis) were repeatedly administered amphetamines over multiple hours or days and observed within controlled conditions (35-37). Most participants exhibited paranoia often accompanied by threatening hallucinations, such as overhearing people plotting against them; these experiences often led participants to become highly anxious, uncooperative, and aggressive.

More recent large-scale case-control and cross-sectional surveys have reinforced persecutory delusions, auditory and visual hallucinations and referential delusions as the most prevalent symptoms of MAP in both clinical and community-based samples (28, 38-41). Relative to earlier work, these studies have also reported a much wider range of methamphetamine-associated symptoms, including olfactory and tactile hallucinations, delusions of control, grandiosity, and mindreading, and disorganised behaviour, speech and thought processes (conceptual disorganisation). These studies also highlighted the prominence of affective disturbance in MAP, particularly within in-patient samples (42, 43),

who reported very high rates of depressive symptoms (up to 91%), anxiety (up to 63%), hostility (up to 84%), and symptoms of suicidality (up to 69%).

Negative psychotic symptoms have been reported in a minority of people with MAP; however, it remains unclear whether these symptoms are due to the effect of methamphetamine or to other confounding factors. Negative psychotic symptoms are characterised by a blunting or loss of normal capacities for speech, motor function, affect, social engagement, and motivation. Srisurapanont and colleagues (44, 45) examined the lifetime prevalence of negative psychotic symptoms among 168 in-patients with MAP (from Australia, Japan, Thailand, and the Philippines), and identified poverty of speech, psychomotor retardation, and flattened affect in 20–26% of patients. Negative symptoms have been reported at similar rates in clinical samples recruited from Australia and the United States (46, 47). Importantly, most patients in these studies had been interviewed within two weeks of methamphetamine use and while on a regime of antipsychotic medications. Thus, negative symptoms in this population may be attributable to methamphetamine withdrawal (which occurs during the first two weeks of detoxification) or the side effects of antipsychotic medications, which can produce secondary negative symptoms such as affective blunting and social withdrawal (18, 48). Accordingly, a recent study by McKetin and colleagues (40) examined the psychiatric symptoms among 164 regular methamphetamine users recruited from the Australian community, and found no evidence that negative psychotic symptoms are exacerbated by methamphetamine use.

Duration of Symptoms in MAP

Most episodes of MAP are transient and resolve within one month after drug cessation; however, a minority of individuals (9–39%) experience symptoms that persist for several months or even years (28, 38, 39). The (typically) transient nature of MAP is best

documented in experimental studies. Participants (most with no prior history of psychosis) rapidly developed an acute psychotic reaction upon methamphetamine administration, which resolved within one week after intoxication. In a review of 111 patients admitted to hospital with MAP, Fashipour and colleagues (28) found that the mean duration of psychotic symptoms was 17 days after hospitalisation, and a vast majority of cases resolved in less than one week (17%), between 1 – 2 weeks (29%), or between 2 – 4 weeks (45%). However, a small proportion (9%) experienced persistent symptoms that continued beyond this one-month timeframe. The proportion of individuals with persistent psychotic symptoms was even larger in a Japanese sample of 104 MAP inpatients: around one-third were hospitalised with persistent symptoms for 1–3 months (10% of cases), 3–12 months (16%) or longer (4%) (39). Japanese researchers have long posited that chronic methamphetamine use can elicit states of "prolonged" (1–6 months) or "persistent" psychosis (over 6 months), and that these represent syndromes that are distinct from transient forms of MAP (49).

Recurrence of MAP episodes

MAP is often a recurrent syndrome in people with chronic methamphetamine use. The first reported case of recurrent MAP was described in 1950, involving a man who was rehospitalised with MAP multiple times over 6 years (31). In each instance, a relapse into methamphetamine use triggered an abrupt re-emergence of paranoia, "excitement," and psychomotor agitation that subsided within one week of hospitalisation. This cyclical pattern is common: a Japanese study of patients admitted to hospital with MAP found that almost half had experienced at least one prior episode, with some having experienced ten prior episodes (50). In such cases, individuals often report an identical profile of symptoms across subsequent episodes (50-53). Symptoms of MAP can return after a single administration of methamphetamine, in smaller doses than initially used, and even after an extended period of abstinence from the drug (54-59). In some cases, people with a history of MAP report a re-

emergence of psychotic symptoms when exposed to psychosocial stress, even without further methamphetamine use. This long-term vulnerability to psychosis is likely due to dopaminergic sensitisation (51, 60), a phenomenon that occurs when repeated or excessive stimulation of the dopamine system (e.g., through methamphetamine use) precipitates a hypersensitivity to further dopaminergic stimulation (e.g., psychosocial stress). This positive feedback mechanism produces a hyper-dopaminergic state, which according to the dopamine hypothesis of psychosis (61), can play a causal role in the development of positive psychotic symptoms.

Diagnostic Criteria for MAP

A diagnosis of MAP is currently based on the criteria for substance-induced psychotic disorder outlined within the DSM-5 (18) or the International Classification of Diseases version 11 (62). A person diagnosed with MAP must experience delusions or hallucinations that develop during or soon after intoxication or withdrawal from methamphetamine. The disturbance must not be better explained by a primary psychotic disorder, evidenced when symptoms resolve within “about one month” (DSM-5) or six months (ICD-11) after drug intoxication. Positive psychotic symptoms must result in clinically significant distress or functional impairment. These criteria imply that individuals may not necessarily meet the full diagnostic criteria for MAP if they experience some psychotic symptoms associated with methamphetamine intoxication or withdrawal, depending on clinical judgement of the impact and intensity of symptoms.

Other forms of substance-induced psychoses

The DSM-5 criteria for substance-induced psychotic disorder outlines a range of illicit and prescription drugs that can prompt psychotic symptoms (18), including alcohol, cannabis, phencyclidine (PCP), other hallucinogens (i.e. LSD), inhalants, sedatives, hypnotics, cocaine,

and other stimulants. Cannabis-related psychosis often involves delusions of persecution, auditory or visual hallucinations, obsessive ideation, confusion, interpersonal sensitivity, agitation, depression, and anxiety (167). Psychosis associated with alcohol (otherwise known as alcohol hallucinosis) is more limited to verbal hallucinations, paranoia, and depressive disturbances (168). A predisposition to psychosis appears to play a greater role in the development of cannabis-associated psychosis compared to MAP. Many individuals who experience psychosis related to cannabis use begin using the drug shortly before psychosis onset (175). Cannabis-related psychosis is more likely to involve a chronic course than MAP 175), and there is a greater risk of transition to schizophrenia (123). By contrast, alcohol-induced psychosis usually occurs only after months or years of prolonged heavy alcohol consumption among those with moderate or severe alcohol dependence (18, 168). People with alcohol-related psychosis have the lowest risk of transition to schizophrenia compared to other forms of substance-induced psychoses (123).

Part C: Differentiating MAP from schizophrenia (SZ)

When people who use methamphetamine present with acute psychotic symptoms, clinicians need to determine whether symptoms are attributable to methamphetamine use (MAP) or to an undiagnosed primary psychotic disorder that is endogenous to the person (63, 64), such as schizophrenia (SZ). A diagnosis of SZ (Table 2) requires the presence of delusions, hallucinations, or disorganised speech, which can occur in the presence of other non-required symptoms (catatonia, disorganised behaviour, and negative symptoms) that may also constitute a diagnosis of SZ. The diagnostic criteria differentiates SZ from MAP, in that positive psychotic symptoms must persist for at least one month (precluding a diagnosis of MAP), and must not be better explained by non-organic factors, such as substance use or a medical condition (e.g., a brain tumour) (18).

Table 2. Summary of DSM-5 criteria for substance-induced psychosis and SZ

Substance-Induced Psychosis (i.e. MAP)	Schizophrenia
A. Presence of one or both of the following symptoms: 1. Delusions. 2. Hallucinations.	A. Presence of at least two of the following symptoms (must include 1, 2, or 3) for a one-month period: 1. Delusions. 2. Hallucinations. 3. Disorganised speech. 4. Grossly disorganised or catatonic behaviour. 5. Negative symptoms.
B. There is evidence from the history, physical examination, or laboratory findings that (1) symptoms developed during or soon after substance intoxication or withdrawal, and (2) the substance involved is capable of producing these symptoms.	B. There has been a marked decrease in functioning in one or more major areas (i.e. work, relationships, self-care) since the onset of the disturbance.
C. The disturbance is not better explained by a psychotic disorder that is not substance-induced. Evidence of an independent psychotic disorder could include (i) the symptoms preceded the onset of the substance use, (ii) symptoms persist for a substantial period of time (e.g., about 1 month) after withdrawal or intoxication, or (iii) a history of recurrent psychotic episodes that are not substance-related.	C. Continuous signs of disturbance for at least 6 months, which includes at least 1 month of psychotic symptoms.
D. The disturbance does not occur exclusively during the course of a delirium.	D. The disturbance is not attributable to schizoaffective disorder and depressive or bipolar disorder with psychotic features.
E. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.	E. The disturbance is not attributable to the physiological effects of a substance or another medical condition. F. The disturbance is not attributable to autism spectrum disorder or a communication disorder.

In reality, it can be extremely challenging for clinicians to provide a reliable and accurate diagnosis of MAP or SZ, as both of these disorders are often expressed as recurrent syndromes with similar profiles of psychiatric symptoms. Misdiagnosis can have serious and long-term implications for treatment and prognosis (65). People with a misdiagnosis of SZ may have their substance use overlooked and be placed on unnecessary long-term regimes of antipsychotic medication, which can have significant lasting side effects including metabolic, motor and hormonal abnormalities (66). A misdiagnosis of MAP among those with undetected SZ may lead to exclusion from early-psychosis intervention or specialist treatment, and duration of untreated psychosis is one of the strongest predictors of poor prognosis among people with psychotic disorders (67). The following section will outline some of the major complications in differentiating MAP from SZ.

Methamphetamine use and SZ

Considerable epidemiological evidence demonstrates an overlap between methamphetamine use and primary psychotic disorders: the rate of stimulant use disorder is 9% among people with psychotic disorders (compared to 3% of the Australian general population (68)), and conversely, the rate of SZ is 10% in people who use methamphetamine (relative to 1% in the general population (69)). This presents a challenge for clinicians who must distinguish those with SZ from the substantial number of people with MAP.

A diagnosis of SZ is appropriate when symptoms are not better accounted for by methamphetamine use; evident when the onset of psychotic symptoms precede initiation of methamphetamine use or persist during periods of abstinence. However, determining the causal and temporal relationship between methamphetamine use and psychotic symptoms is often difficult, as methamphetamine use can alter the onset and clinical course of SZ (48, 70). Some argue that the use of psychoactive substances, such as methamphetamine, can precede

and precipitate the onset of an initial psychotic episode in some people with a predisposition to develop SZ. In a recent population-based cohort study, Callaghan and colleagues (71), examined hospital records for people with no prior history of psychosis who were readmitted after initial hospitalisation (up to ten years later). Those with methamphetamine abuse or dependence (*n*=72,324) had a nine-fold risk of subsequently being diagnosed with SZ relative to people in the control (appendicitis) group, and a 1.5 to 2.8-fold risk relative to individuals who used cocaine, alcohol, or opioids. Moreover, it can be difficult to pinpoint the onset of a psychotic disorder, as subtle prodromal symptoms often manifest for months or years before a first frank psychotic episode (64). Clinicians can struggle to retrospectively determine whether psychotic symptoms preceded the initiation of methamphetamine use in cases where methamphetamine exposure was a potential precipitating factor.

Exposure to psychostimulants can worsen delusions and hallucinations in people with SZ (72). Experimental studies have demonstrated that the administration of prescription amphetamines to people with SZ can exacerbate existing positive symptoms in 70% of those with an active psychotic episode, and precipitate a re-emergence of positive symptoms in 30% of those recovering from a psychotic episode (72). This suggests that people with undiagnosed SZ experience psychotic symptoms that emerge with methamphetamine use, and these individuals would present to healthcare services in much the same manner as individuals with MAP. Importantly, the relationship between methamphetamine use and symptoms of SZ has not been examined in regards to real-world patterns of illicit methamphetamine use, which is likely to be more sustained, chaotic, and intensive than experimental administration. It is unclear how illicit methamphetamine use may alter the symptom profile of people with SZ, and this lack of understanding may further complicate the task of distinguishing methamphetamine-precipitated SZ from MAP.

Similarities in Symptom Profiles

Connell first asserted that MAP "may be indistinguishable from acute or chronic paranoid schizophrenia," and since, numerous clinicians and researchers have described virtually identical symptom profiles among people with MAP and SZ (34, 73-77). Delusions and hallucinations are the only symptom criteria for a diagnosis of MAP (Table 1), however, these are also diagnostic criteria for SZ ((18)). This is particularly problematic as the most dominant symptoms of both disorders include persecutory delusions, reference delusions, and auditory and visual hallucinations (76, 78). Although disorganised speech and grossly disorganised behaviour are diagnostic features of SZ (18), but not MAP, these symptoms are observed in both disorders. Using differential item functioning analysis, Srisurapanont and colleagues (45) found that the severity of positive psychotic symptoms was almost identical among people with MAP (n=169) relative to people with SZ (n=169). Likewise, Medhus (79) demonstrated that people with methamphetamine-related psychoses (n=9) exhibited positive and disorganised symptoms at the same rate of severity and prevalence as people with SZ who screened negative for methamphetamines (n=33). This implies that clinicians cannot reliably differentiate MAP from SZ based on the presence or absence of positive and disorganised symptoms alone.

Negative psychotic symptoms are one (of five) symptom criteria listed for SZ, but they are not featured in the symptom criteria for MAP. As such, particular debate has focused on whether these symptoms could be a point of distinction between the two disorders (40, 49). Although negative symptoms are not required for a diagnosis of SZ, and are observed in only a minority of people with SZ (23–27%) (80), several studies have reported negative symptoms to be markedly more prevalent and severe among patients with SZ compared to patients with MAP (49, 81, 82). This suggests that people who present with significant negative symptoms may be more likely to have an underlying primary psychotic disorder rather than MAP. Conversely, others have observed no differences in the severity of

negative symptoms between people with MAP and SZ (45), and have reported that the prevalence rate of negative symptoms among people with MAP (20–26%) is comparable to that observed in SZ (44, 47). The possible role of negative psychotic symptoms in the differential diagnostic process warrants further clarification.

MAP and SZ as a Single Psychosis

The overlap in the clinical characteristics between MAP and SZ had led some researchers to challenge the current conceptualisation of MAP as a unique disorder distinct from SZ, and instead to propose that these disorders constitute a single clinical entity. Bramness and colleagues (83) argue that MAP represents a precipitation of SZ, in that methamphetamine acts as a trigger to precipitate an underlying predisposition to SZ in vulnerable drug-takers. This hypothesis is underpinned by the diathesis-stress model of psychiatric disorders (77), which posits that psychiatric disorders result from an interaction between internal vulnerabilities (e.g. genes) and environmental stressors (e.g. methamphetamine exposure) over the lifespan (78). A low level of methamphetamine use is needed to trigger a psychotic episode for people with high dispositional vulnerabilities to developing psychosis (i.e. genetic risk for SZ), whereas an extreme level of methamphetamine exposure is needed to catalyse a psychotic episode in people with low psychotic vulnerabilities. In this model, MAP and SZ share common aetiopathological processes and represent quantitative (rather than qualitative) differences on one disease continuum.

This model is consistent with findings by Chen and colleagues (84), who report that methamphetamine users with a history of MAP are five-times more likely to have a family member with SZ relative to users without a history of MAP, implying overlapping genetic risk factors between the two disorders. If these conditions do constitute one clinical disorder,

the current process of assigning people to non-overlapping categories of MAP or SZ may unnecessarily complicate the diagnostic process by imposing artificial boundaries between these disorders. Exploring distinctions between the psychiatric symptom profiles of MAP and SZ will inform an understanding of the conceptual relationship between these disorders, and may improve differential diagnosis and treatment outcomes for people who use methamphetamine.

Part D: Utility of data-driven statistical techniques for understanding psychiatric symptom profiles

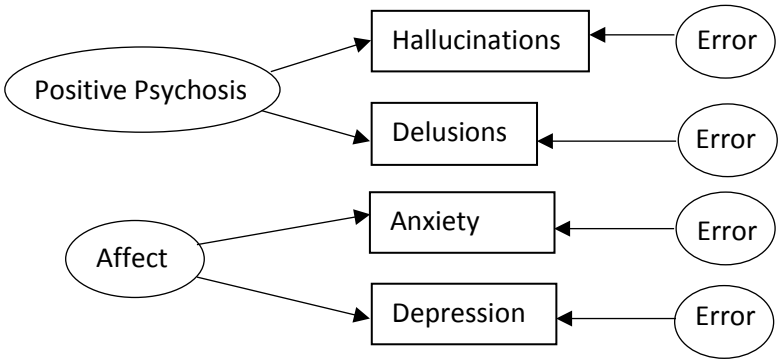
Sophisticated data-driven techniques provide novel methods that may identify more subtle differences in psychiatric symptoms between people with MAP and SZ. Data-driven statistical techniques are used to empirically explore the underlying (latent) theoretical structure of a phenomenon within multivariate data. Latent constructs cannot be directly observed (85, 86), but are statistically inferred by examining the relationships between measured variables (i.e. psychiatric symptoms). Two powerful data-driven techniques include factor analysis, used to identify latent groupings of variables (i.e. factors), and latent class analysis, used to identify latent groupings of respondents (i.e. classes). Preliminary factor analyses have demonstrated that psychiatric symptoms in MAP may have different underlying factor structure to that typically observed in SZ (40, 44). A small number of latent class analyses suggest that there are separate classes (or psychiatric symptom profiles) among people within the methamphetamine-using population (40, 87). The following section will explain these statistical techniques, and outline how they have been previously used to understand the profile of psychiatric symptoms associated with methamphetamine use.

Factor Analysis

Factor analysis examines the bivariate correlations between observed variables (i.e. psychiatric symptoms) to identify smaller groups of highly inter-correlated variables that represent underlying factors (also referred to as dimensions) (88, 89). For example, in a hypothetical dataset containing variables for five psychiatric symptoms (depression, anxiety, delusions, and hallucinations), participants with high ratings of depression may also rate highly on anxiety (forming an "affect" factor), and those who rate highly on hallucinations also rate highly on delusions (forming a "positive psychosis" factor). The factor analysis model (Figure 1) assumes that these symptoms vary together because they are the product of common underlying pathologies (unmeasured latent construct), and additional error due to unreliability in measurement (90). Factor analyses can be exploratory, where there is no imposition of a preconceived structure on the outcome and directly derives factors based on relationships in the data; or confirmatory, which is used to verify a model of factor structure that has been hypothesised a-priori based on existing theory or empirical research (91).

Exploratory factor analysis examines inter-item correlations and attempts to explain as much common variance as possible with each derived factor (91). Factor loadings indicate the degree of association between each variable and each derived factor, essentially conveying how much each variable contributes to that factor. The factors are rotated to identify a model with the maximum number of high factor loadings and the minimum number of cross-loadings (in which a variable loads onto multiple factors) (91). The method of rotation depends upon whether factors are assumed to be correlated (oblique) or uncorrelated (orthogonal) with one another. Determining the number of extracted factors involves a degree of subjective judgement based on the strength of relationships between the variables and factors (factor loadings); and balance between explanatory power (greatest

Figure 1. The factor analysis model



explained common variance) and parsimony (simplest model) (91, 92). Extracted factors should have a common conceptual meaning that is distinct from other factors. Interpretation of each factor can be aided by reviewing the variables with the highest factor loadings and these are considered most representative of the factor. Individual factor scores (e.g. affect score) can be calculated for each respondent in the data, which reflects that person's responses across each variable once it has been weighted against each factor (92, 93).

In confirmatory factor analysis (90, 92), the model can be constrained to conform to a particular structure based on pre-existing hypotheses about the relationships between the measured variables (e.g. an expectation that the model will find a two-factor structure representing positive psychosis and affect). Indices of model fit measure the discrepancy between the expected and observed covariance between the variables (goodness of fit). Principal components analysis is a related data-reduction technique (93), which examines the covariance between variables to identify a small number of unique index components which represent the most individual variation in the measured data. Whereas factor analysis assumes that the latent construct (e.g. "positive psychosis" factor) is driving the variance in the measured variables (e.g. delusions and hallucinations), principal components analysis instead assumes that variance in symptoms is driving the latent construct (derived

components). Unlike factor analysis, principal components analysis does not incorporate a specific error term for each variable into the derived principal components (93).

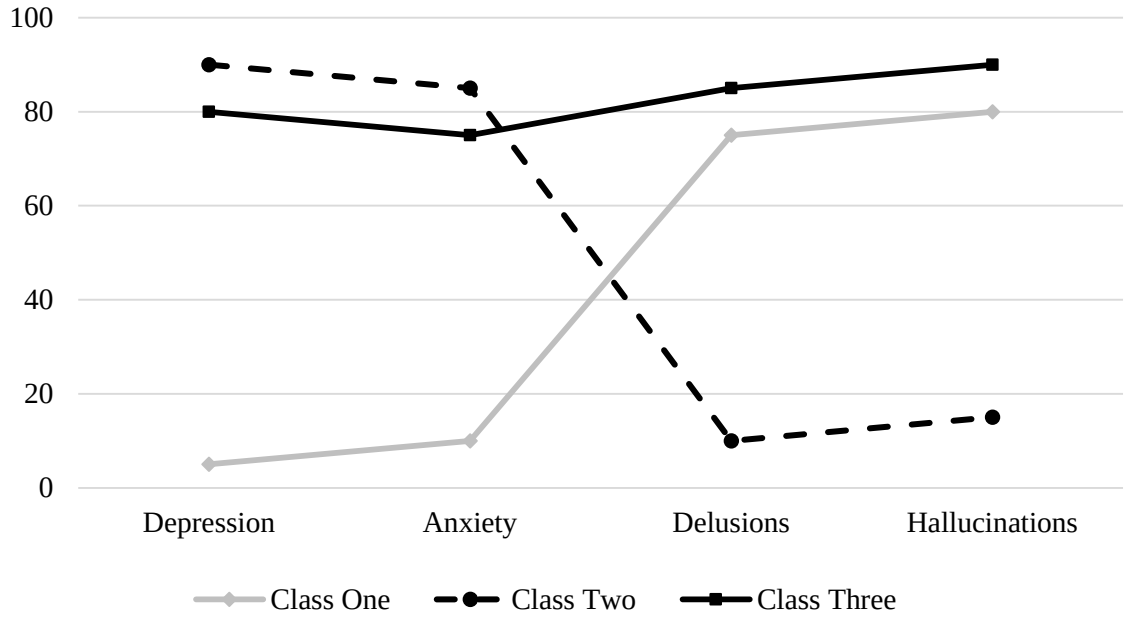
Factor Analysis and MAP

Factor analysis may be useful in exploring the structure of psychiatric symptoms among people who use methamphetamine, and preliminary evidence indicates that a different factor structure may underlie MAP relative to SZ. Factor analyses of people with psychotic disorders (particularly SZ) have generally identified four broad factors: Positive psychotic symptoms (i.e. hallucinations, suspiciousness), affect (i.e. anxiety, depression), negative psychotic symptoms (i.e. blunted affect, emotional withdrawal, motor retardation), and activation (i.e. excitement, motor hyperactivity). These four factors differ in their associations with genetic, cognitive, and neurobiological correlates (94-99). Given the potential aetiological differences between substance-induced and primary psychotic disorders, these classic factors may not accurately represent the underlying structure of symptoms in MAP. A recent exploratory factor analysis by McKetin and colleagues (40) found that psychiatric symptoms exacerbated by methamphetamine use were represented by three factors (positive psychosis, affective symptoms, and psychomotor agitation), and unlike the structure of SZ, there was no evidence of a negative psychotic factor. Using principal components analysis, Srisurapanont and colleagues (44), found that hallucinations and delusions merged with incoherent speech to form a single positive/disorganised factor underlying MAP. Previous studies that have compared SZ and MAP on these classic four factors may have failed to discern subtle differences between these disorders due to differing underlying factor structures.

Latent Class Analysis

Latent class analysis (binary variables) and latent profile analysis (continuous variables) are used to split seemingly heterogeneous data into smaller homogeneous groups of people (i.e. classes or subpopulations of individuals) who exhibit similar patterns of response profiles (e.g. psychiatric symptoms) (100). Whereas factor analysis is used to identify groups of variables to derive underlying factors, latent class/profile analysis is used to identify groups of respondents (cases) to identify mutually exclusive classes of people. A hypothetical three-class model (Figure 2) may distinguish between people with delusions and hallucinations (class one, 30% of cases), depression and anxiety (class two, 50% of cases), or all these symptoms (class three, 20% of cases).

Figure 1. Hypothetical three-class model



This statistical process attempts to extract mutually exclusive groups by maximising between-class differences and minimising the within-class differences (101). Using the maximum likelihood method, the maximum probability of each individual's membership to each class is estimated and used to allocate that individual to a particular class (102). The

analysis calculates the probability that an individual will provide a certain response on an item (i.e. the likelihood of reporting a specific symptom) given the individual's class membership (item response probabilities). To determine the number of latent classes underlying the data, successive models that specify a greater number of latent classes, are generated. The goodness of fit for each successive model is compared to the previous model. The aim is to identify the model with the highest accuracy and goodness of fit, strongest explanatory power, and most parsimonious structure (101, 103). The final model should extract classes that appear conceptually meaningful and interpretable.

LCA can be catagorised as a type of cluster analysis – a broad umbrella term that can be used to describe a family of related statistical techniques that divide data into groupings based on measures of distance between data points (169). These techniques include also include hierarchical cluster analysis and K-means cluster analysis, which have been used in prior research (170, 171) to understand groupings of people based on their clinical characteristics. LCA offers several key advantages over these other clustering techniques. Hierarchical cluster analysis can only be applied to dichotomous data and k-means cluster analysis can only be applied to interval or ratio data, whereas LCA can accommodate all types of data (172, 173). LCA offers several indices of goodness of fit that assist the researcher in determining the optimal number of clusters (such as the Bayesian Information Criterion), whereas there are no such diagnostics for K-means cluster analysis and hierarchical cluster analysis (172, 173). In sum, LCA is a type of cluster analysis that is particularly powerful and flexible when compared to other types of cluster analyses.

Latent Class Analysis and MAP

There is preliminary evidence of distinct classes (or profiles/syndromes) of psychiatric symptoms associated with methamphetamine use. Using latent class analysis,

Bousman and colleagues (87) identified three profiles of positive psychotic symptoms among people dependent on methamphetamine and who did not meet criteria for SZ. Classes were characterised by persecutory delusions (class one); hallucinations and persecutory delusions (class two); or hallucinations, persecutory delusions, and delusions of reference, control and thought passivity (class three). That is, class three reported a more severe symptom profile with higher rates of "bizarre" delusions, which are linked to a higher risk of psychotic disorder and have historically been considered indicative of SZ (104). The profiles (or syndromes) identified by Bousman and colleagues (87) varied in degree of similarity to the profile typically observed in SZ. By not differentiating these separate profiles of psychosis (particularly those more similar to SZ), prior research may have obfuscated subtle differences between the symptom profiles of MAP and SZ. Further research is needed to understand how people with SZ are captured within profiles of psychosis in this population, and whether these individuals would share an overlapping latent symptom profile with people who have MAP.

Part E: The current research

Summary of the Issues

Psychotic symptoms are experienced by a considerable proportion of people who use methamphetamine (105), and it can be challenging for clinicians to determine whether these symptoms are attributable to methamphetamine-associated psychosis, primary psychotic disorders (such as SZ), acute methamphetamine intoxication or withdrawal, or another comorbid psychiatric disorder. Accurate diagnosis of these conditions is crucial to ensuring appropriate treatment, adequate support, and overall better outcomes for people who use methamphetamine and experience psychotic symptoms (65). The ability for clinicians to differentiate MAP from other conditions has been hindered by a lack of consistent detailed

data into the profile of psychiatric symptoms observed in MAP. Symptoms of MAP have often been measured using broad psychiatric symptom categories (i.e. positive, negative, disorganised, and affective symptoms (45, 69, 79) that might not accurately reflect the underlying factor structure of psychiatric symptoms among people with MAP. In particular, it is unclear whether negative symptoms are a core component of MAP or attributable to secondary factors (such as the side effects of medication) (40, 47). Detailed studies that document the specific symptoms associated with MAP have generated widely discrepant prevalence rates for certain psychotic symptoms (e.g. first rank delusions, tactile hallucinations (28, 38, 106)) and certain psychiatric symptoms (conceptual disorganisation, depression (37, 42, 76, 107)) among this population. Many previous attempts (38, 69, 76, 106) to differentiate the psychiatric symptom profile of MAP from SZ have primarily used traditional methods of analysis (such as pairwise group comparisons) to compare the cross-sectional symptom profiles of MAP and SZ; an approach that has not identified reliable differences between these disorders.

In this thesis, I explore the application of data-driven techniques to provide a more sophisticated understanding of the psychiatric symptom profile associated with methamphetamine use. Factor analysis can be used to establish the underlying factor structure of psychiatric symptoms associated with methamphetamine use, and to examine how the derived factors relate to methamphetamine use. These factor structures cannot be measured when using traditional methods of analysis to examine cross-sectional data, and this technique provides a novel method of clarifying the presence or absence of a negative syndrome in people who use methamphetamine (and do not have SZ).

Latent class analysis can be used to identify discrete profiles (or syndromes) of psychiatric symptoms underlying the population of people who use methamphetamine. These latent profiles cannot be detected when measuring the rates of specific psychiatric

symptoms averaged across a sample. Prior research may have recruited people who represent different distributions of these profiles, and delineating between these separate symptom profiles may reconcile the wide variations in prevalence rates previously reported for specific psychiatric symptoms. Although a small number of latent class analyses have been used to identify discrete symptom profiles among people who use methamphetamine (87); no prior research has examined how these empirically-derived syndromes correspond to the current diagnostic constructs of MAP and SZ. If the diagnostic categories of MAP and SZ correspond to separate latent profiles, this approach may identify novel differences in specific psychiatric symptoms between these groups that cannot be observed through traditional methods of analysis. From a theoretical standpoint, this finding would also support the need for separate diagnostic classifications for SZ and MAP. Alternatively, if the diagnostic groupings of MAP and SZ correspond to a single psychotic syndrome with a shared symptom profile, which would align with the argument (108) that MAP represents a precipitation of SZ.

Aims and Outline of the Current Thesis

The overarching aim of this thesis was to clarify the profile and underlying structure of psychotic symptoms among people who use methamphetamine. In doing so, I intended to provide greater insight into potential distinctions between the psychiatric symptom profile of people with methamphetamine-associated psychoses (MAP) relative to people with schizophrenia (SZ). This objective was addressed in a series of studies, with five key research questions:

Research Question 1. Which psychiatric symptoms have been associated with MAP, and what is the typical duration of symptoms in this condition?

A systematic review was conducted to canvas the available literature for the profile and duration of psychiatric symptoms in the MAP syndrome. This review was used to ascertain (i) which psychiatric symptoms have been associated with MAP, (ii) how this symptom profile changes longitudinally, and (iii) the proportion of people who experience psychotic episodes that persist beyond one month after drug cessation (as per the DSM-5 criteria for MAP).

Research Question 2. What is the association between methamphetamine use and psychiatric symptoms among people with primary psychotic disorders?

In study two, the association between methamphetamine use and psychiatric symptom prevalence was examined among people with primary psychotic disorders, specifically SZ and affective psychotic disorders. The past-year prevalence for specific psychiatric symptoms was compared among people who have used methamphetamine during the past 12 months relative to people who have not.

Research Question 3. What is the underlying factor structure of psychiatric symptoms among people who use methamphetamine (and do not have SZ)?

In study three, exploratory factor analysis was used to examine the structure of current psychiatric symptoms in people who use methamphetamine and do not meet lifetime criteria for SZ. This analysis was used to investigate the presence of a negative symptom syndrome and to examine how this syndrome relates to methamphetamine use.

Research Question 4. Are there distinct profiles of positive psychotic symptoms among people who use methamphetamine, and how do these profiles correspond to the diagnostic criteria for SZ?

In study four, latent class analysis was used to examine latent classes (or profiles) of delusions and hallucinations rated across the lifetime in a sample of people who have used methamphetamine in the past month, including those who met criteria for SZ. Follow-up analyses were used to investigate how the derived latent symptom profiles correspond to the diagnosis category of SZ.

Research Question 5. Are there distinct profiles of psychiatric symptoms among people who use methamphetamine, and how do these profiles represent people with SZ and people with MAP?

In study five, latent class analysis was used to examine latent classes (or profiles) of positive psychotic, affective, disorganised/activation, and negative symptoms rated in the past-month among people who have used methamphetamine at least monthly. Follow-up analyses were conducted to investigate how these profiles represent people who meet diagnostic criteria for SZ relative to those who meet diagnostic criteria for MAP.

The findings from these five studies are synthesised in a final discussion chapter, in which I review possible implications for the diagnosis and clinical management of psychotic symptoms among people who use methamphetamine.

Study One: A systematic review of the symptom profile and course of methamphetamine-associated psychosis.

This study has been published as following journal article:
Voce, A., McKetin, R., Calabria, B., Burns, R., & Castle D. (2019). A systematic review of the symptom profile and course of methamphetamine associated psychosis. *Substance Use and Misuse*, 54(4): 549-559.

Foreword:

Study one addressed the first research question of this thesis: *Which psychiatric symptoms have been associated with MAP, and what is the typical duration of symptoms in this condition*? This systematic review was conducted to establish what is already known within the existing literature. This study synthesised the available literature for (i) specific psychiatric symptoms in the MAP syndrome, and (ii) the proportion of people who experience persistent psychotic episodes that continue beyond one month after drug cessation (thereby exceeding the duration criteria for MAP defined in the DSM-5). The relevant MAP literature spans over 60 years, and to account for evolving diagnostic classifications across this time, I used broad inclusion criteria to capture people who were diagnosed with MAP or were identified as having MAP by the authors. Likewise, in recognising that different methodologies would bias the symptom profiles reported, I incorporated a wide range of research types into this review, including case-control, cross-sectional, experimental, case report, and longitudinal studies.

SUBSTANCE USE & MISUSE
2019, VOL. 54, NO. 4, 549–559
https://doi.org/10.1080/10826084.2018.1521430

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

A Systematic Review of the Symptom Profile and Course of Methamphetamine-Associated Psychosis

Alexandra Voce[a], Bianca Calabria[b,c], Richard Burns[a], David Castle[d,e], and Rebecca McKetin[c,f]

[a]Centre for Research on Ageing, Health and Wellbeing, Australian National University, Acton, Australia; [b]National Centre for Epidemiology and Population Health, Australian National University, Acton, Australia; [c]National Drug and Alcohol Research Centre, University of New South Wales, Randwick, Australia; [d]St Vincent's Hospital, Fitzroy, Australia; [e]Department of Psychiatry, University of Melbourne, Melbourne, Australia; [f]National Drug Research Institute, Curtin University, Perth, Australia

ABSTRACT

Objectives: The psychiatric symptom profile of methamphetamine-associated psychosis (MAP) has varied considerably across studies of different research designs. We performed a systematic review to examine the available evidence for specific psychotic symptoms associated with MAP, including the clinical course and longitudinal changes in this symptom profile. *Methods*: Five key electronic databases were searched to identify studies that examined the symptom profile or clinical course of MAP in individuals identified as having MAP. The reporting of specific psychiatric symptoms, and duration of symptoms where available, was recorded for each study. *Results*: Ninety-four articles were identified ($n = 7387$), including case-control ($k = 29$), cross-sectional ($k = 20$), experimental ($k = 6$), case report ($k = 29$), and longitudinal ($k = 20$) studies. Persecutory delusions, auditory and visual auditory hallucinations were by far the most commonly reported symptoms (reported in 65–84% of studies). Hostility, conceptual disorganization, and depression were reported in a large proportion of studies (31–53%). Negative symptoms were mostly absent (<20%). The median percentage of participants with persistent psychotic symptoms (>1 month duration) across studies was 25% (excluding case reports). *Conclusion*: Persecutory delusions, auditory and visual hallucinations, hostility, depression and conceptual disorganization are central to MAP, whereas negative psychotic symptoms are typically absent. An overrepresentation of institutionalized or male participants may have overemphasized negative symptoms and underreported affective symptoms in past research. Symptoms of MAP may persist beyond one month after drug cessation in some individuals. Clinicians are encouraged to manage affective symptoms in MAP individuals, and monitor for the development of chronic psychotic symptoms.

KEYWORDS

Amphetamine; stimulants; substance induced psychotic disorder; clinical presentation; duration; persistent

Introduction

Methamphetamine is a highly addictive synthetic psychostimulant used by an estimated 36 million people globally (United Nations Office on Drugs & Crime, 2016). A number of serious negative physical and psychiatric outcomes are associated with heavy or long-term use of methamphetamine or its derivative amphetamine (henceforth collectively referred to as methamphetamine unless otherwise specified). One of the most well-documented effects of heavy methamphetamine use is a transient psychotic state referred to as methamphetamine-associated psychosis (MAP; Glasner-Edwards et al., 2014; Grant et al., 2012), which is reported in approximately 23% of individuals who regularly use the drug (McKetin, McLaren, Lubman, & Hides, 2006). A diagnosis of MAP is currently based on the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5) criteria for substance-induced psychosis, which requires an individual to present with either delusions or hallucinations (i.e., positive symptoms) that abate within approximately one month of drug cessation (American Psychiatric Association, 2013). Although clinical profile and duration of psychotic symptoms is central to a diagnosis of MAP, methodological heterogeneity across studies

CONTACT Alexandra Voce alexandra.voce@anu.edu.au Centre for Research on Ageing, Health and Wellbeing, Australian National University, Room 1.16, Building 54, Mills Road, Florey, ACT 2601, Australia.

Supplemental data for this article can be accessed here.

have produced conflicting findings into these clinical characteristics.

Well-established symptoms of MAP include auditory and visual hallucinations and delusions of persecution, as well as hostility, anxiety and hyperactivity (Bell, 1973; Ellinwood, 1967; McKetin et al., 2016a). The role of other psychotic symptoms in MAP is less clear, and prevalence rates have varied substantially for specific subtypes of symptoms, for instance, first-rank delusions (thought withdrawal, insertion, broadcasting, or external control) and tactile hallucinations (Chen et al., 2003; Ellinwood, 1967; Fasihpour et al., 2013). Particular attention has been paid to the existence of a negative syndrome in MAP patients (Tomiyama, 1990; Srisurapanont et al., 2011). McKetin et al. (2016a) examined the factor structure of psychiatric symptoms exacerbated by current methamphetamine use over a 12-month period in a sample of dependent users. Symptoms clustered on three dimensions: positive psychotic symptoms (i.e., delusions and hallucinations); affective symptoms (e.g., depression and hostility); and psychomotor agitation (e.g., bizarre/disorganized behavior and motor hyperactivity), however, no evidence for negative symptoms was found. These findings contrast with Ali and et al (2011), who observed poverty of speech, psychomotor retardation and flattened affect in 26% of inpatients with MAP.

Critical to a diagnosis of "substance induced psychotic disorder" in the DSM-V (American Psychiatric Association, 2013) is the qualification that the psychotic disturbance must not be better explained by a primary psychotic disorder (such as schizophrenia). Cases in which positive psychotic symptoms precede substance use or persist for at one month or more after acute drug intoxication are suggested to be evidence of primary psychotic disorders. While psychotic symptoms induced by methamphetamine are typically transient and resolve within one month of acute intoxication (Bell, 1965; Chen et al., 2003), evidence indicates that a minority of chronic users experience a form of persistent MAP that may continue for several months or years (Chen et al., 2005; McKetin et al., 2016b; Tomiyama, 1990). Iwanami et al. (1994) reported on 104 psychiatric inpatients with "amphetamine delusional disorder" (DSM-III-R equivalent of MAP) and did not meet criteria for schizophrenia. Despite ongoing abstinence and antipsychotic pharmacotherapy, 27% experienced symptoms lasting beyond on month and 17% experienced symptoms lasting over three months. Resolving these empirical inconsistencies is essential as the profile and duration of psychotic symptoms are fundamental to our present conceptualization of MAP (American Psychiatric Association, 2013).

Despite 60 years of research examining the symptom profile of MAP (Connell, 1958), no previous systematic review has documented and synthesized the available evidence for specific psychiatric symptoms in this syndrome. A clearer understanding of these clinical characteristics may provide greater accuracy when differentiating MAP from other psychotic disorders, assist clinicians in planning holistic and integrated treatment to address the various co-occurring psychiatric issues associated with MAP, and provide important insights into underlying aetiopathological mechanisms.

This systematic review examines the literature on MAP, to ascertain which psychotic symptoms have been associated with MAP and how this symptom profile changes longitudinally. In addition, we will examine the clinical duration of MAP symptoms by determining the proportion of participants who experience MAP episodes that persist beyond one month after drug cessation as per DSM-5 criteria.

Method

Search strategy

To ensure a systematic and explicit process of study identification and selection, we conformed to the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines (Figure 1; Table S1 in Supplementary Material). With the assistance of an experienced librarian, five electronic databases were searched (PsychINFO, Medline, PubMed, Scopus, and Ovid) for articles published up to 14 March 2018. All searches combined the two conceptual domains: methamphetamine or amphetamine, and psychotic symptoms. Both studies of methamphetamine and amphetamine were included due to their overlapping physiological effects (Martin, Sloan, Sapira, & Jasinski, 1971) and difficulties in reliably distinguishing between these compounds in the illicit drug market (McKetin, McLaren, & Kelly, 2005). When available, subject headings were exploded and combined. For example, the Medline search involved: "Methamphetamine" (exp), "Amphetamine" (exp), "Amphetamine-related disorders" (exp), *amphetamine$", *amfetamine$, methamphetamine$, methylamphetamine$; AND Substance-Induced Psychoses" (exp), "psychotic", "psychos$s", "Hallucinations" (exp), "Delusions" (exp), "Paranoi*", "mania". The search was limited to peer-reviewed empirical studies which were published in English language journals with human

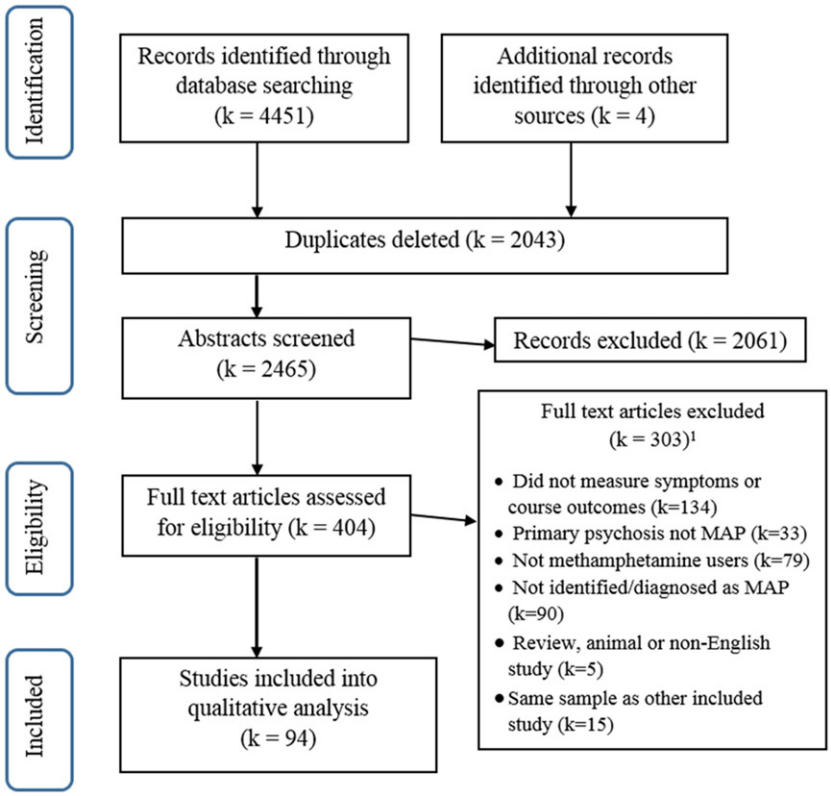


Figure 1. PRISMA flow diagram of article search and selection process. Note. 1. Numerous articles are listed under multiple justifications.

subjects. Documents such as reviews, commentaries, unpublished papers, and book chapters were excluded. Latest editions of key journals, subject reviews and the reference lists of papers were hand-searched to locate studies not identified by the electronic search. A total of 4455 papers were identified through the electronic database search ($k = 4451$) and hand-search ($k = 4$). After removal of duplicates ($k = 2043$), abstracts of the remaining 2464 papers were screened.

Inclusion criteria

To be eligible for inclusion, studies had to examine the profile or clinical duration of MAP symptoms in participants who (i) were explicitly identified as having symptoms of MAP by the authors, (ii) were diagnosed with MAP, or (iii) had been diagnosed with substance-induced psychosis and currently used methamphetamine or amphetamine. Abstracts were screened for relevance based on the inclusion criteria and all full text articles ($k = 404$) were judged for eligibility by one reviewer (A.V). A second reviewer (R.M) then independently assessed 85% of full-text articles ($k = 336$) for eligibility. Initial agreement between the reviewer ratings was 88%. Disagreements were resolved by discussion and consensus between A.V and R.M ($k = 42$), and judgement by a third reviewer (R.B) where necessary. Where multiple articles assessed the same population, only articles with the most detailed description of the symptom profile was selected ($k = 15$ excluded). Case-control studies involving participants with and without MAP were included only if the data for MAP participants could be extracted separately. Included studies are listed in Table S2 in Supplementary Material.

Data extraction

As studies reported symptoms in different scales and units of measurement, we reduced the findings of each study to a basic binary measure (symptom present (1) or symptom absent (0)). We collated a list of psychotic symptoms that were measured in the reviewed studies. Each study was examined to determine whether it measured each specific psychotic symptom and whether this symptom was reported as present or absent in the sample. A symptom was categorized as present when it was reported as a prevalence or scale score for the sample or when the symptom was explicitly noted in a case description.

These findings thus reflect the available evidence for the presence of a symptom, and do not reflect their severity.

Data on symptom duration differed across research designs. For case-control, experimental, cross-sectional and longitudinal studies, information on the duration of symptoms was extracted from the studies if it were possible to calculate the proportion of individuals experiencing persistent symptoms (one month after the cessation of drug use). In addition, we also calculated the maximum number of days taken for symptoms to abate in experimental studies. For case studies, we calculated the proportion of individuals for which symptoms lasted less than one week, 1–4 weeks, 1–6 months, or over 6 months.

Results

Study characteristics

Overview of studies

A total of 94 eligible studies were identified with a total of 7387 participants, including 20 cross-sectional surveys, 29 case-control surveys, ten longitudinal surveys, and 29 case reports (with 49 individual cases). There were also six experimental studies in which participants were administered methamphetamine under laboratory conditions to induce psychotic symptoms. Case report and experimental studies were primarily conducted in the USA (48%), with some articles from the UK (11%) and Japan (11%); whereas longitudinal, case-control and cross-sectional survey studies were primarily conducted in Japan (38%), with fewer studies from Australia (13%), the USA (10%) and Iran (8%). Includes studies ranged in publication date from 1949 to 2018. Sample sizes (excluding case studies) varied depending on the research design and ranged widely from 4 to 1112 participants (interquartile range, $IQR = 16–151$). In the experimental studies, doses of methamphetamine ranged from 5mgs to 274 mgs and were administered either once off, once per hour for several hours or several days; or every 6 h for several hours or days. Length of follow up in longitudinal studies ranged from 3 months to 16 years), with 54–100% of participants retained at follow-up (IQR). The substance of interest as per the inclusion criterion included methamphetamine (63%, $k = 59$), amphetamine (16%, $k = 15$), both amphetamine and methamphetamine (9%, $k = 8$), or prescription amphetamines (32%, $k = 30$). Full details of the study characteristics for each study design are available in Tables S3–S7 in Supplementary Material.

Participant demographics

Studies typically had a majority of male participants ($IQR = 70–90\%$) and the mean age ranged between 29 and 37 years (IQR). Seventy-two percent of studies recruited inpatients or outpatients from hospitals or psychiatric units. Other studies recruited from drug treatment services (11%), prisons (5%), community settings (4%), or private practitioners (3%). Forty-five percent of studies reported the proportion of participants who were identified as having methamphetamine dependence, use disorders, abuse, or addiction (henceforth collectively referred to as dependence) based on criteria from the DSM or International Statistical Classification of Diseases and Related Health Problems (ICD; World Health Organization, 1992). The mean rate of dependence when reported was typically very high (median =99%).

Diagnosis or identification of MAP

All study participants were identified as having symptoms of MAP, but only 65% of studies gave participants an explicit diagnosis of MAP or substance-induced psychosis. A diagnosis of MAP was particularly uncommon in case report studies (18%) and did not occur in any experimental studies. The DSM (American Psychiatric Association, 2013) was the most commonly used classification system to diagnose MAP ($k = 23$), whereas nine studies used versions of the ICD (World Health Organization, 1992), and five studies employed both the ICD and DSM systems. One study used the Chinese Classification of Mental Disorders Version 3 (CCMD-3; Chinese Medical Association, 2004).

Measurement of symptoms

The use of standardized scales to measure psychiatric symptoms was reported in 4% of case studies, 40% of experimental studies, 48% of case-control studies, 50% of cross-sectional studies, and 80% of longitudinal studies. The range of rating scales encompassed the Brief Psychiatric Rating Scale ($k = 9$; Overall & Gorham, 1962), the Positive and Negative Syndrome Scale ($k = 3$; Kay, Fiszbein, & Opler, 1987), the MINI International Neuropsychiatric Interview ($k = 3$, Sheehan et al., 1998), the Methamphetamine Experience Questionnaire ($k = 2$; Leamon et al., 2010), the Scale for the Assessment of Negative Symptoms ($k = 3$; Andreasen, 1983), the Scale for the Assessment of Positive Symptoms ($k = 2$; Andreasen, 1984), the Composite International Diagnostic Interview ($k = 1$; CIDI; Cooper, Peters, & Andrews, 1998) and the

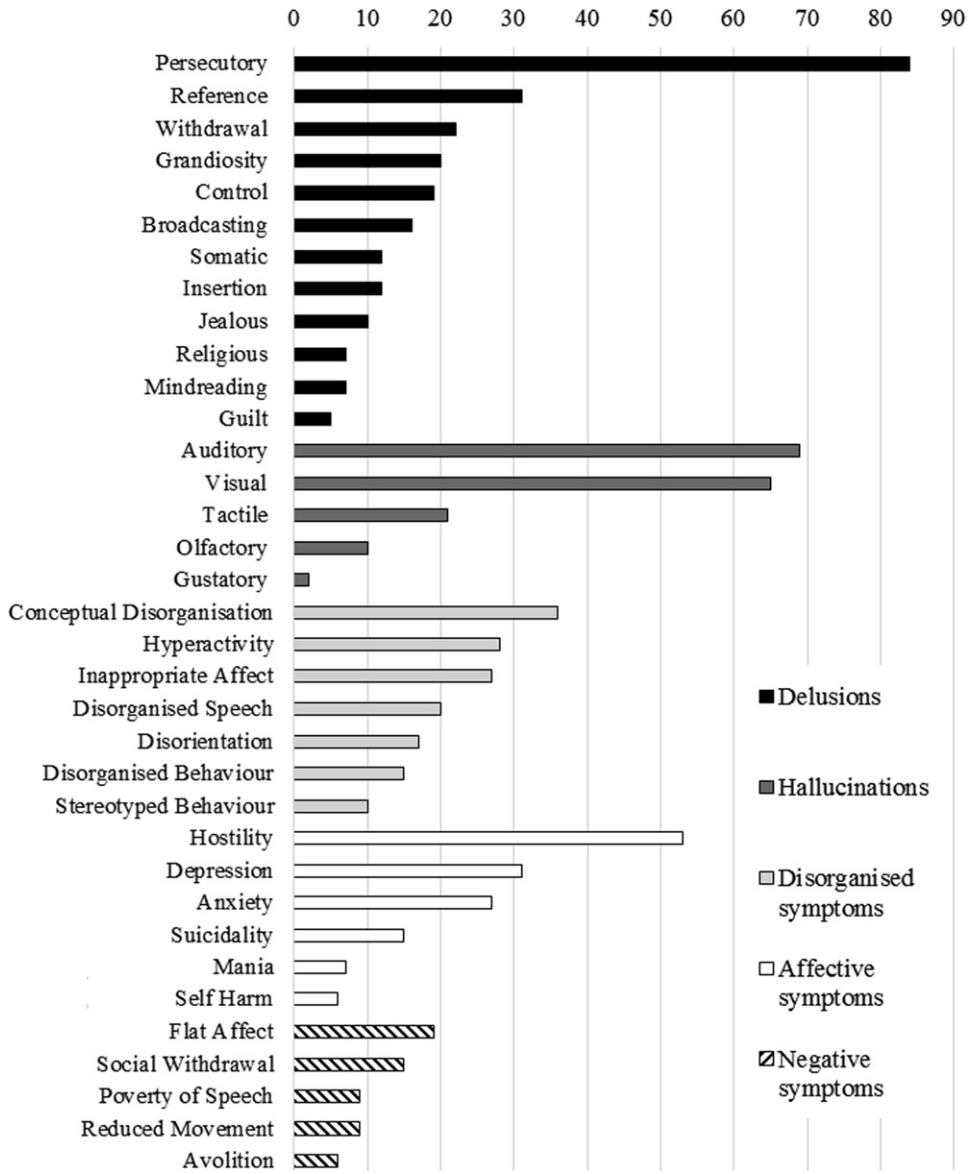


Figure 2. Percentage of total studies reporting each symptom.

Structured Clinical Interview for DSM-IV ($k = 2$; SCID; First, Spitzer, Gibbon, & Williams, 2002).

Profile of psychiatric symptoms

As shown in Figure 2, the most commonly reported symptoms across all study types were delusions of persecution (reported in 84% of studies), auditory hallucinations (69% of studies) and visual hallucinations (65% of studies). Relatively fewer studies reported delusions with non-persecutory themes, ranging from 5% (delusions of guilt) to 31% (delusions of reference), or hallucinations in other sensory modalities (21% tactile, olfactory 10%, gustatory 2%). Hostility was recorded in 53% of studies. Other commonly reported symptoms included conceptual disorganization (36% of studies), depression (31% of studies), hyperactivity (28% of studies), inappropriate affect (27% of studies) and anxiety (27% of studies). Flat affect was reported in 19% of studies, while other negative symptoms were reported in 6 to 15% of studies.

Variation in psychiatric symptoms by study design

Reporting of specific psychiatric symptoms varied among studies with different methodological design and sample characteristics, such as mean age, gender ratio, and recruitment method (Table 1). A wide range of psychiatric symptoms were reported in the experimental studies. Compared to other study designs, a higher proportion of these studies reported disorganized psychotic symptoms (100% compared to

Table 1. Proportion (%) of studies reporting psychiatric symptoms by study design.

	CC	CS	Lon	Exp	Case
Any positive symptom	87	80	83	100	98
Any hallucination	69	85	83	80	73
Auditory hallucinations	69	65	83	60	49
Visual hallucinations	62	60	50	40	51
Persecutory delusions	69	75	83	80	67
Reference delusions	37	35	33	20	18
Any first-rank delusion	31	40	67	60	2
Any non-persecutory delusion	56	55	83	60	53
Any disorganized symptom	37	60	50	100	61
Conceptual disorganization	12	35	33	40	22
Inappropriate affect	12	35	17	40	20
Disorganized speech	6	15	17	60	16
Disorganized behavior	6	40	0	40	2
Any affective symptom	25	50	50	100	85
Hostility	19	50	17	80	51
Depression	25	35	33	40	20
Anxiety	19	25	0	60	22
Any negative symptom	25	20	50	60	22

Note. Study design includes case-control (CC), cross-sectional (CS), longitudinal (Lon), experimental (Exp), and case reports (Case).

[cf.] 37–61%), particularly disorganized speech (60% cf. 6–17%), any affective symptoms (100% cf. 25–85%), particularly hostility (80% cf. 17–51%) and anxiety (60% cf. 0–25%). Cross-sectional studies typically aimed to document a detailed symptom profile of MAP, whereas case-control studies typically aimed to compare MAP with schizophrenia on the core positive symptoms of psychosis. Compared to case-control studies, a greater proportion of cross-sectional studies measured and reported affective (50% cf. 25%) and disorganized symptoms (60% cf. 37%), particularly disorganized behavior (40% cf. 6%). Fifty percent of longitudinal studies reported negative symptoms compared to 20–25% of case-control and cross-sectional studies. A single case study (2%) reported first-rank delusions (i.e., thought withdrawal, broadcasting, insertion, control, mindreading), compared to 31–67% of other study designs.

Compared with male-majority samples, samples in which female participants outnumbered male participants reported more affective symptoms (60% cf. 33%), particularly depression (50% cf. 18%), but fewer negative psychotic symptoms (0% cf. 24%). Participants recruited from prisons, community settings, drug treatment services or private practitioners reported fewer disorganized (23% cf. 46%) and negative psychotic symptoms (8% cf. 24%) compared to those recruited from inpatient or outpatient clinical samples. No noteworthy differences in the symptoms profiles were observed between other study characteristics, such as country of origin and diagnostic process.

Duration of symptoms

Twenty-seven studies reported the percentage of participants who experienced persistent psychotic symptoms (>1 month after abstinence), including 12 case-control, five cross-sectional, four longitudinal, and six experimental studies. The overall median prevalence of persistent symptoms across these studies was 25%. This rate varied by study design, geographic location, and diagnostic classification system used. There were no cases of persistent symptoms in experimental studies, and the maximum amount of time for symptoms to abate once the final amphetamine dose was administered ranged from 12 h to 7 days. In contrast, longitudinal studies reported persistent symptoms in a median 40% of participants (range 14–96%).

Almost half of case-control, cross-sectional, longitudinal and experimental studies that reported duration of symptoms were conducted in Japan (41%, $k = 11$): in these studies, persistent symptoms were found in a median 44% of participants (range 18–96%). A much lower prevalence rate of 12% (ranging 0–39%) was reported in fourteen studies conducted in the USA, Australia, Canada, Iran and broader Asia. The difference in prevalence rates between Japanese and non-Japanese studies was statistically significant ($t = 4.79$, $p = .0001$). Japanese studies primarily used the ICD-10 system (35%) over the DSM-IV system (25%), whereas few non-Japanese studies employed the ICD-10 (6%) relative to the DSM-IV (42%).

Twenty-four case studies reported on the duration of symptoms after participants ceased methamphetamine use (i.e., when admitted to hospital), with persistent symptoms identified in two participants (8%). Symptoms persisted for 1–4 weeks in most cases (58%; $k = 14$), while 36% of participants ($k = 8$) experienced symptoms for one week or less.

Longitudinal changes in symptom profile

Longitudinal changes in the profile of MAP symptoms were reported in four studies, with mixed results; positive symptoms reduced over time in three studies and remained stable in the fourth study, whereas negative symptoms were stable in three studies and increased in the fourth study. Yeh, Lee, Sun, and Wan (2001) found a reduction in most positive symptoms and stable rates of most negative symptoms when assessing a sample of former MAP patients who had successfully avoided rehospitalization over a 7-month period, half of whom abstained from methamphetamine use. Tomiyama (1990) measured abstinent patients hospitalized for MAP who were prescribed antipsychotic medication, which can produce secondary negative symptoms (Tandon, Nasrallah, & Keshavan, 2009). Over a 4-month period, Tomiyama

(1990) found longitudinal decreases in positive symptoms and increases in negative symptoms. Over a 3-year period, Sato, Chen, Akiyama, and Otsuki (1983) examined individuals who were continually hospitalized for psychotic reactions to methamphetamine and found stable rates of positive and negative symptoms. Javadian, Shabani, and Shariat (2016) measured psychotic symptoms across a three month period in a sample of former MAP patients, comparing those who remained abstinent and those who relapsed to methamphetamine use. Across the total sample, positive symptoms decreased while negative symptoms remained stable, except for those who reused methamphetamine, in whom positive symptoms increased over time.

Three longitudinal studies reported the frequency at which participants with an initial MAP diagnosis eventually transition to a diagnosis of schizophrenia. Similar rates were reported by Kittirattanapaiboon et al (2010; $k = 1116$) and Medhus et al. (2015; $k = 28$) who found that 33–38% were re-diagnosed with schizophrenia after 6–7 years, while a lengthier study of 825 patients found 16% transitioned to schizophrenia within 16 years (Niemi-Pynttäri et al., 2013).

Discussion

This is the first systematic review to examine the symptom profile, duration and longitudinal changes in psychotic symptoms associated with MAP. We identified a profile of symptoms primarily consisting of persecutory delusions, auditory and visual hallucinations, and to a lesser extent, hostility, conceptual disorganization, depression and hyperactivity. Negative symptoms were mostly absent from this profile. These symptoms mirror the symptom constellation identified in early foundational experiments into the MAP syndrome (AAngrist & Gershon, 1970; Bell, 1973; Jonsson & Sjostrom, 1970), and our findings align with the symptom profile with the factor structure of MAP symptomology identified by McKetin et al. (2016a), which included positive psychotic symptoms, affective symptoms, and symptoms of psychomotor agitation (i.e., hyperactivity).

Negative psychotic symptoms

Few studies (6–19%) reported negative psychotic symptoms—such as flat affect, poverty of speech, avolition, reduced motor activity, and social withdrawal—supporting the argument that negative symptoms are not characteristic of MAP (McKetin et al., 2016a). Alternatively, the profile of negative symptoms may change over the course of MAP to gradually resemble that observed in schizophrenia. Very few longitudinal studies have examined the long-term symptom trajectory of MAP, but those that have done so, indicate that positive symptoms may decrease while negative symptoms may stabilize or increase over time (Sato et al., 1983; Tomiyama, 1990; Yeh et al., 2001). This pattern is well-recognized in individuals with chronic schizophrenia and has been associated with gradual neurodegeneration which can occur over the course of psychotic disorders (Foussias, Agid, Fervaha, & Remington, 2014; Tandon et al., 2009). Neurodegeneration may also occur with prolonged methamphetamine use (Chen et al., 2015). Further research is needed to confirm whether negative symptoms increase over time, and to investigate whether this change is associated with a greater risk of transitioning to schizophrenia later in life.

Affective symptoms

The range of affective dysregulation associated with MAP (e.g., hostility, depression, inappropriate affect) reflects the significant reciprocal relationships between affective disorders, psychotic disorders and methamphetamine use (Darke, Kaye, McKetin, & Duflou, 2008; Hartley, Barrowclough, & Haddock, 2013; Koreen et al., 1993), and supports previous arguments that affective symptomology is a core component of MAP (McKetin et al., 2016a; Tsuang, Simpson, & Kronfol, 1982), as seen in other psychotic disorders such as schizoaffective disorder (American Psychiatric Association, 2013). Consistent with epidemiological research into sex differences in affective disorders (Altemus, Sarvaiya, & Epperson, 2014), depression was more commonly reported in female-majority samples compared to male-majority samples. Over half the reviewed studies reported symptoms of hostility. Methamphetamine use has been associated with a dose-related increase in violence, and risk of violent behavior is especially high in those with severe or persistent psychotic symptoms (McKetin, McLaren, Lubman, & Hides, 2008; McKetin et al., 2014). These findings highlight the need for clinicians to assess, acknowledge and effectively manage affective and arousal symptoms in individuals with MAP.

Duration of psychotic symptoms

It has been long debated whether MAP constitutes a psychotic reaction attributable to exclusively to the

psychotomimetic properties of the drug, or whether MAP occurs when methamphetamine acts as a stressor and precipitates primary psychotic in individuals with predisposition to psychotic illness (Bramness et al., 2012; van Os, 2014); the observed heterogeneity in duration of psychotic symptoms implies that both these clinical states may exist within the methamphetamine-using population. Experimental studies appear to demonstrate a psychotic state attributable primarily to methamphetamine use, as most (otherwise healthy) participants exhibited psychotic symptoms upon a sufficiently large dosage of the drug and these symptoms resolved within one week after drug administration. On the other hand, an average of 25% of participants experienced "persistent MAP," in which symptoms extended beyond the DSM timeframe of "about 1 month" after acute intoxication (American Psychiatric Association, 2013) and were likely precipitated by factors beyond mere methamphetamine exposure. Cases of persistent MAP were significantly more likely in Japanese—relative to non-Japanese—studies, which typically used the ICD classification (World Health Organization, 1992) to exclude individuals with primary psychotic disorders (i.e., cases of psychosis persisting for over 6 months after drug intoxication).

Many researchers have asserted the existence of a persistent form of MAP which is appears to be etiologically separate from transient MAP (Chen et al., 2005; McKetin, Baker, Dawe, Voce, & Lubman, 2017; McKetin et al., 2016b), and subtle differences are observed in risk factors and symptom profiles—indicating potentially different pathogenic pathways—between transient and persistent MAP (Chen et al., 2005; McKetin et al., 2017; McKetin et al., 2016b). In contrast, similarities in symptom profiles and risk factors between schizophrenia and persistent MAP suggest that this condition may constitute drug-precipitated schizophrenia. Further research is needed to investigate the validity and characteristics of persistent MAP and individuals with MAP should be closely monitored for the development of chronic psychotic symptoms in clinical settings.

Limitations of the reviewed studies

Many of the reviewed studies did not adjust for factors known to influence psychotic symptom severity (McKetin, Lubman, Baker, Dawe, & Ali, 2013), particularly, poly-drug use, frequency and duration of methamphetamine use, and antipsychotic medication use. The dosages and frequency of methamphetamine use were likely underreported or misrepresented in survey and case study designs due to an overreliance on self-report measures (Rosay, Skroban Najaka, & Herz, 2007). Although undermined by serious ethical issues, experimental studies were able to overcome self-report limitations and observe participants transition through a wide range of symptoms over many hours or days. Nonetheless, the validity of experimental studies is limited by failures to use the use standardized scales to measure psychiatric symptoms, and failure to employ standardized diagnostic tools to exclude those with possible primary psychotic disorders. Certain symptoms reported by most experimental studies, particularly hostility and anxiety, were likely exacerbated by prolonged and continuous confinement in the laboratory setting. Finally, experimental studies may not have replicated the symptomology associated with chronic or heavy methamphetamine use which often occurs in a binge pattern over several days, weeks or months (Cho & Melega, 2002).

A majority of studies recruited from inpatient settings, and likely missed methamphetamine users with milder or more transient symptoms who may not seek medical assistance. As a result, the derived symptom profile may reflect more severe or complex pathology than is typical for the broader population of methamphetamine users. Similarly, an average of only 20–30% of participants were female in the included studies. This disparity is likely due to sampling error rather than a heightened risk of MAP among males, as a recent systematic review of factors associated with psychotic symptoms in adults using methamphetamine found no association between MAP and gender (Arunogiri, Foulds, Mcketin, & Lubman, 2018). The current study did not directly compare symptom profiles between males and females, however, some limited evidence suggests that prevalence of specific psychotic symptoms in methamphetamine users is moderated by sex (Mahoney, Hawkins, De La Garza, Kalechstein, & Newton, 2010), and research into sex differences in schizophrenia also indicates that negative symptoms may be more likely in males whereas affective symptoms may be more likely in females (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Overall, an overrepresentation of institutionalized males in the MAP literature may have underestimated affective symptoms and overestimated negative psychotic symptoms in the MAP symptom profile.

None of the reviewed studies examined the length of psychotic symptoms in community methamphetamine users, most likely due to difficulties in verifying periods of methamphetamine abstinence. As such, the

extent and impact of persistent MAP symptoms in this population is widely unknown, and future research should explore symptom profile and duration in community samples of methamphetamine users with a particular focus on those earlier in their drug use trajectory (i.e., recreational users).

Limitations of the current review

A key limitation of this systematic review is that the included studies often focused on symptoms that are considered representative and diagnostic of MAP (i.e., delusions), and a greater number of studies measured (and thus reported) these symptoms relative to symptoms considered less characteristic of MAP (such as stereotyped behavior). Second, these results do not reflect the exact prevalence rate of specific symptoms in MAP population. Studies reported symptoms in different scales and units of measurement, and as such, consolidation into the current review required these diverse findings to be reduced to a basic binary measurement (symptom present or absent). As a result, studies that reported low prevalence or high prevalence of a given symptom were both coded as "symptom present." Finally, studies of disparate quality were aggregated into the present review without differential weighting against indicators of study quality (such as sample size).

Future research may build upon this review by using meta-analytic techniques (i.e., meta-regression) to examine the interacting relationships between symptom profiles and different study characteristics (i.e., sample population, sex ratio, mean age, location of study) whilst systematically adjusting for variations in the methodological quality.

Conclusions

The current review employed broad inclusion criteria to extract the profile of psychotic symptoms associated with MAP from an extensive collection of studies. The symptom profile of MAP consists of persecutory delusions, auditory and visual hallucinations, hostility, depression, and conceptual disorganization. Negative symptoms do not appear characteristic of MAP. Symptoms may persist beyond one month after intoxication in some individuals. Previous research may have underreported depression, and overemphasized negative symptoms, due to a reliance on institutionalized male participants. Clinicians are encouraged to monitor patients for the development of chronic psychotic symptoms and to effectively manage affective symptoms among those with MAP. Further research into the symptom profile and duration of MAP in community methamphetamine users is essential to improving diagnosis, treatment and overall wellbeing in this population.

Acknowledgments

A.V. takes responsibility for the accuracy of the data extraction and analysis.

Disclosure statement

The authors report no conflicts of interests.

Funding

This work was supported by an Australian Postgraduate Scholarship held by A.V.

References

Altemus, M., Sarvaiya, N., & Epperson, C. (2014). Sex differences in anxiety and depression clinical perspectives. *Front Neuroendocrinol*, *35*(3), 320–330.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders, Five Edition*. Arlington, VA: Author.

Andreasen, N. (1983). *The scale for the assessment of negative symptoms (SANS)*. Iowa City: University of Iowa.

Andreasen, N. (1984). *The scale for the assessment of positive symptoms (SAPS)*. Iowa City: University of Iowa.

Angrist, B., & Gershon, S. (1970). The phenomenology of experimentally induced amphetamine psychosis-preliminary observations. *Biological Psychiatry*, *2*, 95–107.

Arunogiri, S., Foulds, J., Mcketin, R., & Lubman, D. (2018). A systematic review of risk factors for methamphetamine-associated psychosis. Australian & New Zealand Journal of Psychiatry, *52*(6), 514–529.

Bell, D. (1965). Comparison of amphetamine psychosis and schizophrenia. *The British Journal of Psychiatry: The Journal of Mental Science*, *111*, 701–707.

Bell, D. (1973). The experimental reproduction of amphetamine psychosis. *Archives of General Psychiatry*, *29*(1), 35–40.

Bramness, J. G., Gundersen, Ø. H., Guterstam, J., Rognli, E. B., Konstenius, M., Løberg, E.-M., … Franck, J. (2012). Amphetamine-induced psychosis: A separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry*, *12*, 221

Chen, C.-K., Lin, S.-K., Chen, Y.-C., Huang, M.-C., Chen, T.-T., Ree, S. C., & Wang, L.-J. (2015). Persistence of psychotic symptoms as an indicator of cognitive impairment in methamphetamine users. *Drug and Alcohol Dependence*, *148*, 158–164.

Chen, C.-K., Lin, S.-K., Sham, P. C., Ball, D., Loh, E.-W., Hsiao, C.-C., … Murray, R. M. (2003). Pre-morbid characteristics and co-morbidity of methamphetamine users

with and without psychosis. *Psychological Medicine*, *33*(8), 1407–1414.
Chen, C., Lin, S., Sham, P., Ball, D., Loh, W., & Murray, R. (2005). Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *136B*(1), 87–91.
Chinese Medical Association (2004). *Chinese Classification and Diagnostic Criteria of Mental Disorder*. 3rd ed. Jinan: Shandong Science and Technology Press.
Cho, A., & Melega, W. (2002). Patterns of methamphetamine abuse and their consequences. *Journal of Addictive Diseases*, *21*(1), 21–34.
Connell, P. (1958). *Amphetamine psychosis*. London: Oxford Press.
Cooper, L., Peters, L., & Andrews, G. (1998). Validity of the Composite International Diagnostic Interview (CIDI) psychosis module in a psychiatric setting. *Journal of Psychiatric Research*, *32*(6), 361–368.
Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug and Alcohol Review*, *27*(3), 253–262.
Ellinwood, E. (1967). Amphetamine psychosis. *I. Description of the Individuals and Process. Journal of Nervous and Mental Disease*, *144*(4), 273–283.
Fasihpour, B., Molavi, S., & Shariat, S. (2013). Clinical features of inpatients with methamphetamine-induced psychosis. *Journal of Mental Health (Abingdon, England)*, *22*(4), 341–349.
First, M., Spitzer, R., Gibbon, M., & Williams, J. (2002). *Structured Clinical Interview for DSM-IV, Research Version*. New York: New York State Psychiatric Institute.
Foussias, G., Agid, O., Fervaha, G., & Remington, G. (2014). Negative symptoms of schizophrenia: Clinical features, relevance to real world functioning and specificity versus other CNS disorders. *European Neuropsychopharmacology*, *24*(5), 693–709.
Glasner-Edwards, S., Mooney, L., Marinelli, C., P., Hillhouse, M., Ang, A., & Rawson, R. (2014). Methamphetamine psychosis: Epidemiology and management. *CNS Drugs*, *28*(12), 1115–1126.
Grant, K., LeVan, T., Wells, S., Li, M., Stoltenberg, S., Gendelman, H., … Bevins, R. (2012). Methamphetamine-associated psychosis. Journal of Neuroimmune Pharmacology, *7*(1), 113–139.
Hartley, S., Barrowclough, C., & Haddock, G. (2013). Anxiety and depression in psychosis: A systematic review of associations with positive psychotic symptoms. *Acta Psychiatrica Scandinavica*, *128*(5), 327–346.
Iwanami, A., Sugiyama, A., Kuroki, N., Toda, S., Kato, N., Nakatani, Y., … Kaneko, T. (1994). Patients with methamphetamine psychosis admitted to a psychiatric hospital in Japan. *Acta Psychiatrica Scandinavica*, *89*(6), 428–432.
Javadian, S., Shabani, A., & Shariat, S. (2016). Clinical course of methamphetamine-induced psychotic disorder in a 3-month follow-up. *Prim Care Companion CNS Disord*, *18*(6). doi:10.1016/j.jsat.2007.12.004
Jonsson, L., & Sjostrom, K. (1970). A rating scale for evaluation of the clinical course and symptomatology in amphetamine psychosis. *British Journal of Psychiatry*, *117*(541), 661–665.
Kay, S., Fiszbein, A., & Opler, L. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, *13*(2), 261–276.
Kittirattanapaiboon, P., Mahatnirunkul, S., Booncharoen, H., Thummawomg, P., Dumrongchai, U., & Chutha, W. (2010). Long-term outcomes in methamphetamine psychosis patients after first hospitalisation. *Drug and Alcohol Review*, *29*(4), 456–461.
Koreen, A., Lieberman, J., Alvir, J., Mayerhoff, D., Loebel, A., Chakos, M., … Cooper, T. (1993). Depression in first-episode schizophrenia. *American Journal of Psychiatry*, *9*(2-3), 240–1648.
Leamon, M., Flower, K., Salo, R., Nordahl, T., Kranzler, H., & Galloway, G. (2010). Methamphetamine and paranoia: The methamphetamine experience questionnaire. *The American Journal on Addictions*, *19*(2), 155–168.
Mahoney, J., Hawkins, R., De La Garza, R., Kalechstein, A., & Newton, T. (2010). Relationship between gender and psychotic symptoms in cocaine-dependent and methamphetamine-dependent participants. *Gender Medicine*, *7*(5), 414–421.
Martin, W., Sloan, J., Sapira, J., & Jasinski, D. (1971). Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clinical Pharmacology & Therapeutics*, *12*(2part1), 245–258.
McKetin, R., Baker, A., Dawe, S., Voce, A., & Lubman, D. (2017). Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Research*, *251*, 349–354.
McKetin, R., Dawe, S., Burns, R. A., Hides, L., Kavanagh, D. J., Teesson, M., … Saunders, J. B. (2016a). The profile of psychiatric symptoms exacerbated by methamphetamine use. *Drug and Alcohol Dependence*, *161*, 104–109.
McKetin, R., Gardner, J., Baker, A. L., Dawe, S., Ali, R., Voce, A., … Lubman, D. I. (2016b). Correlates of transient versus persistent psychotic symptoms among dependent methamphetamine users. *Psychiatry Research*, *238*, 166–171.
McKetin, R., Lubman, D., Baker, A., Dawe, S., & Ali, R. (2013). Dose-related psychotic symptoms in chronic methamphetamine users: Evidence from a prospective longitudinal study. *JAMA Psychiatry*, *70*(3), 319–324.
McKetin, R., Lubman, D., Najman, J., Dawe, S., Butterworth, P., & Baker, A. (2014). Does methamphetamine use increase violent behaviour? Evidence from a prospective longitudinal study. *Addiction*, *109*(5), 798–806.
McKetin, R., McLaren, J., & Kelly, E. (2005). The Sydney methamphetamine market: Patterns of supply, use, personal harms and social consequences. The National Drug Law Enforcement Research Fund Monograph series (no.13). Syndey, New South Wales: National Drug and Alcohol Research Centre.
McKetin, R., McLaren, J., Lubman, D., & Hides, L. (2006). The prevalence of psychotic symptoms among methamphetamine users. Addiction, *101*(10), 1473–1478.
McKetin, R., McLaren, J., Lubman, D., & Hides, L. (2008). Hostility among methamphetamine users experiencing psychotic symptoms. *American Journal on Addictions*, *17*(3), 235–240.

Medhus, S., Rognli, E., Gossop, M., Holm, B., Mørland, J., & Bramness, J. (2015). Amphetamine-induced psychosis: Transition to schizophrenia and mortality in a small prospective sample. *The American Journal on Addictions*, *24*(7), 586–589.

Niemi-Pynttäri, J., Sund, R., Putkonen, H., Vorma, H., Wahlbeck, K., & Pirkola, S. (2013). Substance-induced psychoses converting into schizophrenia: A register-based study of 18,478 finnish inpatient cases. *The Journal of Clinical Psychiatry*, *74*(01), e94–e99.

Ochoa, S., Usall, J., Cobo, J., Labad, X., & Kulkarni, J. (2012). Gender differences in schizophrenia and first-episode psychosis: A comprehensive literature review. *Schizophrenia Research and Treatment*, *2012*, 1–198.

Overall, J., & Gorham, J. (1962). The brief psychiatric rating scale. *Psychological Reports*, *10*(3), 799–812.

Rosay, A., Skroban Najaka, S., & Herz, D. (2007). Differences in the validity of self-reported drug use across five factors: Gender, race, age, type of drug, and offense seriousness. *Journal of Quantitative Criminology*, *23*(1), 41–58.

Sato, M., Chen, C., Akiyama, K., & Otsuki, S. (1983). Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biological Psychiatry*, *18*, 429–440.

Sheehan, D., Lecrubier, Y., Sheehan, K., Amorim, P., Janavs, J., & Weiller, E. (1998). The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *Journal of Clinical Psychiatry*, *59*, 22–33.

Srisurapanont, M., Arunpongpaisal, S., Wada, K., Marsden, J., Ali, R., & Kongsakon, R. (2011). Comparisons of methamphetamine psychotic and schizophrenic symptoms: A differential item functioning analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *35*(4), 959–964.

Tandon, R., Nasrallah, H., & Keshavan, M. (2009). Schizophrenia, "Just the facts" 4. Clinical features and conceptualization. *Schizophrenia Research*, *110*(1–3), 1–23.

Tomiyama, G. (1990). Chronic schizophrenia-like states in methamphetamine psychosis. *Psychiatry and Clinical Neurosciences*, *44*(3), 531–539.

Tsuang, M., Simpson, J., & Kronfol, Z. (1982). Subtypes of drug abuse with psychosis. Demographic characteristics, clinical features, and family history. *Archives of General Psychiatry*, *39*(2), 141–147.

United Nations Office on Drugs and Crime (2016). *World drug report*. New York: United Nations.

van Os, J. (2014). The many continua of psychosis. JAMA Psychiatry, *71*, 985–986.

World Health Organization. (1992). *ICD-10 Classification of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines*. Geneva: Author.

Yeh, H., Lee, Y., Sun, H., & Wan, S. (2001). Six months follow-up of patients with methamphetamine psychosis. *Chinese Medical Journal*, *64*, 388–394.

Study Two: The relationship between illicit amphetamine use and psychiatric symptom profiles in schizophrenia and affective psychoses

This study has been published as following journal article:
Voce, A., McKetin, R., Burns, R., Castle D., & Calabria, B. (2018). The relationship between illicit amphetamine use and psychiatric symptom profiles in schizophrenia and affective psychoses. *Psychiatry Research*, 265: 19-24.

Foreword:

Study two addressed the second research question of this thesis: *What is the association between methamphetamine use and psychiatric symptoms among people with primary psychotic disorders*? In this study, I explore whether methamphetamine use is associated with differences in the prevalence of specific psychiatric symptoms among people with schizophrenia (SZ) and affective psychotic disorders. I explored the relationship between methamphetamine use and symptom prevalence separately for those with SZ (*n*=347) and those with affective psychoses (*n*=289), as these two diagnostic groups are characterised by distinct psychiatric symptoms profiles. Psychiatric symptoms among a sample of past-year methamphetamine users (*n*=205) were compared against a control sample of lifetime users (*n*=431) who had not used methamphetamine for at least 12 months. These findings provide greater insight into how illicit methamphetamine may exacerbate or precipitate psychiatric symptoms among people with primary psychotic disorders, which may facilitate efforts to distinguish cases of methamphetamine-precipitated SZ from cases of MAP.

Psychiatry Research 265 (2018) 19–24

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

The relationship between illicit amphetamine use and psychiatric symptom profiles in schizophrenia and affective psychoses

Alexandra Voce[a,*], Rebecca McKetin[b,c], Richard Burns[a], David Castle[d,e], Bianca Calabria[f,c]

[a] Centre for Research on Ageing, Health and Wellbeing, Australian National University, Building 54, Mills Road, Acton, ACT 2601, Australia
[b] National Drug Research Institute, Curtin University, 10 Selby Street, Shenton Park, Perth, WA 6845, Australia
[c] National Drug and Alcohol Research Centre, University of New South Wales, 22-32 King Street, Randwick, NSW 2031, Australia
[d] St Vincent's Hospital, 41 Victoria Parade, Fitzroy, VIC 3065, Australia
[e] Department of Psychiatry, University of Melbourne, Grattan St, Melbourne, VIC 3010, Australia
[f] National Centre for Epidemiology and Population Health, Australian National University, Building 62, Mills Road, Acton, ACT 2601, Australia

ARTICLE INFO

Keywords:
Methamphetamine
Stimulants
Primary psychotic disorders
Bipolar disorder
Substance use
Hallucinations
Delusions

ABSTRACT

This study examines whether illicit amphetamine use is associated with differences in the prevalence of specific psychiatric symptoms in a community sample of individuals diagnosed with schizophrenia or affective psychotic disorders. Data was drawn from the Australian Survey of High Impact Psychosis. The Diagnostic Interview for Psychosis was used to measure substance use and psychiatric symptoms. Participants had used amphetamine within their lifetime and had an ICD-10 diagnosis of schizophrenia (n = 347) or an affective psychotic disorder (n = 289). The past year prevalence of psychiatric symptoms was compared among those who had used amphetamine in the past year (past-year use, 32%) with those who had not (former use, 68%). Univariate logistic regression analysis indicated that past-year users with schizophrenia had a significantly higher past year prevalence of hallucinations, persecutory delusions, racing thoughts, dysphoria, and anhedonia relative to former amphetamine users with schizophrenia. There were no significant differences in symptoms between past-year and former users with affective psychotic disorders. The relationship between amphetamine use and specific psychiatric symptoms varies across different psychotic disorders. Amphetamine use may hinder prognosis by exacerbating symptoms of schizophrenia through dopaminergic dysfunctions or depressive vulnerabilities, however, this needs to be confirmed by prospective longitudinal research.

1. Introduction

Illicit amphetamine use is associated with poorer functioning and prognosis in persons with primary psychotic disorders, such as schizophrenia spectrum disorder (Lambert et al., 2005; Schimmelmann et al., 2012). Prevalence rates of methamphetamine and amphetamine (hereafter referred to collectively as amphetamine) use are significantly elevated in those with psychotic disorders relative to the general population (Sara et al., 2015), particularly for those with affective psychotic disorders, such as bipolar disorder (McElroy et al., 2001; Winokur et al., 1998). It is well-documented that prescription amphetamine-type psychostimulants can exacerbate and precipitate hallucinations, delusions and manic symptoms in those with psychotic disorders (Curran et al., 2004), however, it remains unclear whether the use of illicit amphetamines in community settings is associated with meaningful differences exist in the expression of specific psychiatric symptoms.

Curran et al. (2004) systematically reviewed 32 experimental studies in which individuals with schizophrenia were administered prescription psychostimulants which have a similar neuronal action in the brain to amphetamine, such as dexamphetamine or methylphenidate. Delusions and hallucinations (referred to as positive psychotic symptoms) were exacerbated in 70% of participants with active psychoses and precipitated in 30% individuals recovering from a psychotic episode. In a recent study of 2,307 adults with bipolar disorder, Viktorin et al. (2017) found that treatment with methylphenidate significantly increased the risk of hospitalisation with a manic episode. Mania was defined by the International Classification of Diseases 10th revision (ICD-10; World Health Organisation, 1992) and is characterised by elevated mood and symptoms of disorganisation such as inappropriate social behaviour, reckless activity, and distractibility. No field research has examined whether these relationships apply to the illicit use of non-prescription street amphetamine in the broader population of people with psychotic disorders.

* Correspondence to: Centre for Research on Ageing, Health and Wellbeing, Australian National University, Room 1.16, Building 54, Mills Road, Florey, ACT 2601, Australia.
E-mail address: alexandra.voce@anu.edu.au (A. Voce).

https://doi.org/10.1016/j.psychres.2018.04.015
Received 25 October 2017; Received in revised form 3 April 2018; Accepted 4 April 2018
Available online 05 April 2018
0165-1781/

The relationship between psychiatric symptoms and illicit substance use in those with schizophrenia has been examined more generally in several case-control studies. Soyka et al. (2001) found that persons with schizophrenia who use illicit substances were more likely than non-users to exhibit hallucinations and delusions, and less likely to exhibit negative symptoms, however these differences have not been consistently replicated (Stone et al., 2014). Whist few such studies have included persons with affective psychotic disorders, Weiss et al. (2004) reported that those with bipolar disorder often perceive subjective reductions in depression and racing thoughts when using illicit drugs or alcohol. These findings may not reflect the specific relationship between amphetamine use and psychiatric symptoms as the overall results for users of different substances were aggregated in these studies.

Delineating the profile of psychiatric symptoms associated with amphetamine use in persons with psychotic disorders may inform our understanding of how amphetamine use contributes to the burden of psychotic illness and may lead to poorer prognosis in this population. Treatment for psychotic disorders and co-morbid substance use remains a complex challenge (Dixon, 1999; Hunt et al., 2013) and clarifying the relationship between amphetamine use and symptomatology may advise treatment options in this context.

The current study examined whether illicit amphetamine use was associated with differences in the prevalence of specific psychiatric symptoms in a community sample of people with psychotic disorders. Psychiatric symptoms were compared for individuals who had used amphetamine in the past 12 months (referred henceforth as "past-year users") relative to a control sample of individuals who had not used amphetamine for at least 12 months but had at some point within their lifetime (referred henceforth as "former users"). The relationship between amphetamine use and psychiatric symptoms was compared separately for participants with schizophrenia and those with affective psychotic disorders, as these two diagnostic groups are characterised by distinct psychiatric symptoms profiles (American Psychiatric Association, 2013). Amphetamine use is strongly related to specific positive psychotic symptoms (such as persecutory delusions) in otherwise healthy individuals, and as such, we aimed to examine both specific symptoms and broad symptom categories. We expected that the prevalence rate of delusions and hallucinations to be higher in past-year – relative to former – amphetamine users with schizophrenia. Based on findings from Viktorin et al. (2017), we expected the prevalence rate of elevated mood and disorganised symptoms (i.e. inappropriate social behaviour, reckless activity, and distractibility) to be higher in past-year – relative to former – amphetamine users with affective psychotic disorders.

2. Method

2.1. Participants and procedure

Data was drawn from the Australian Survey of High Impact Psychosis (SHIP) (Morgan et al., 2012). Individuals aged 18–64 years were screened for psychosis when contacting public mental health services at seven sites across the five mainland states of Australia in 2010. This sampling frame covered 10% of the Australian population aged 18–64 years (approximately 1.5 million people in catchment area). From the 7955 eligible individuals who screened positive for psychosis, 1825 were randomly selected (via computer generator) and assessed on measures of substance use, psychiatric symptoms, cognitive ability, physical health, medication use, health service use and demographic data. The study was approved by institutional human research ethics committees at each study site, and all participants provided written informed consent prior to interview. Further detail on the SHIP study procedures are reported elsewhere (Morgan et al., 2012). Authors of the current study had access to data for individuals who had used illicit amphetamine within their lifetime (n = 731).

2.2. Measures

2.2.1. Psychiatric diagnosis

Psychiatric history and symptoms were assessed using the Diagnostic Interview for Psychosis (DIP; Castle et al., 2006). Current and lifetime ICD-10 diagnoses (World Health Organisation, 1992) were generated from the DIP using a computer algorithm based on the Operational Criteria Checklist for Psychosis (OPCRIT; McGuffin et al., 1991). ICD-10 diagnoses generated using the DIP (Castle et al., 2006) have substantial interrater reliability (kappa = 0.74), good test-retest reliability (kappa = 0.65), and good convergent validity against the Schedules for Clinical Assessment in Neuropsychiatry (SCAN; Wing et al., 1990). The present study extracted data for individuals who had a current diagnosis of either schizophrenia (n = 347) or an affective psychotic disorder, such as depressive psychosis (n = 26), schizoaffective disorder (n = 135) or bipolar disorder (n = 128). We excluded those with subclinical psychotic symptoms (n = 12) or a diagnosis of non-psychotic depression (n = 46) or delusional disorders (n = 37).

2.2.2. Psychiatric symptoms

Prevalence rates of psychiatric symptoms were assessed in the DIP based on clinical observation, participant self-report and clinical case-notes where available. The current study used past-year ratings for auditory hallucinations (non-verbal, multiple voices, running commentary), delusions (persecution, reference, control, grandiosity and bizarre), affective symptoms (suicidality, dysphoria, anhedonia, elevated mood, and anxiety), disorganised (including manic) symptoms (racing thoughts, distractibility, reckless activity and inappropriate social behaviour). Composite binary variables were created to indicate whether participants had experienced any delusion, hallucination, any affective symptom, or any disorganised symptom.

2.2.3. Substance and medication use

Lifetime and past year use of amphetamines, alcohol, cannabis, tranquilisers, cocaine, hallucinogens and ecstasy were assessed based on self-report. Amphetamines also included methamphetamine and non-prescription dexamphetamine. The frequency of substance use in the past year was scored as daily (or almost daily), weekly (1–2 days per week), monthly (1–3 occasions per month), less than monthly, or no use in past year. The number of participants reporting amphetamine use on a daily, weekly, or monthly basis was too few for reliable ordinal analyses to be conducted separately for each diagnostic group (refer to Supplementary Table 1). Consequently, categories of amphetamine use frequency were collapsed into a binary outcome variable to reflect past-year amphetamine use (any use in past 12 months) and former amphetamine use (no use in past 12 months). With the exception of cannabis, the number of former users reporting illicit substance use was too small for reliable analysis and were merged into one binary "poly-substance use" variable to identify individuals who had used heroin, tranquilisers, cocaine, hallucinogens or ecstasy within the past 12 months. Participants were asked whether they had used any anti-psychotic, antidepressant or mood stabilising medication in the past 12 months.

2.2.4. Demographics characteristics

Demographic measures included current age in years, sex, marital status ('single and never married', 'married or de facto', 'separated, divorced or widowed'), age in years when left school, and employment status over the past 12 months ('employed', 'home duties', 'carer for relatives', 'retired', 'volunteer work', 'student', or 'unemployed').

2.3. Statistical analyses

Two-tailed analyses were conducted using Stata version 14.1 (StataCorp, 2015). The predictor measure was past year prevalence of

each psychiatric symptom and the main outcome variable was past year amphetamine use. Potential confounding variables were defined as variables significantly associated with both the predictor measure and outcome variables. Descriptive comparisons were made using independent sample *t*-tests for continuous variables and Pearson's chi-square tests for binary variables. Pearson's chi-square tests were used to identify unadjusted differences in the prevalence rates of psychiatric symptoms between past-year and former amphetamine, with a stringent alpha value of $p < 0.01$ considered statistically significant to correct for multiple comparisons. Univariate logistic regression was used to estimate the unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CI) of each psychiatric symptom between past-year and former amphetamine users, with alpha values of $p < 0.05$ considered statistically significant.

3. Results

3.1. Sample characteristics

The study sample consisted of 636 participants, 55% ($n = 347$) of whom were diagnosed with schizophrenia and 44% ($n = 289$) with an affective psychotic disorder (Table 1). The median age of participants was 33 years (IQR = 28–40). The majority of participants were male (67%), single and had never been married (67%), and they had a mean of 16 years (SD = 0.12) total education. Sixty-eight ($n = 431$) percent of participants had not used amphetamine within the past year ("former amphetamine users"). Thirty-two percent of participants had used amphetamine in the past year ("past-year amphetamine users"), either less than monthly (58%), on 1–3 occasions per month (19%), 1–2 days per week (15%), or daily/almost daily (9%). Frequency of amphetamine use is reported separately for each diagnostic group in Supplementary Table 1. Past-year users were younger, more likely to be employed in the past 12 months, and reported a shorter duration of psychotic disorder relative to former amphetamine users. Past-year users were more likely than former users to report frequent alcohol consumption, use illicit substances in addition to amphetamines in the past 12 months (Table 1), and meet criteria for lifetime diagnosis of cannabis abuse or dependence.

3.2. Association between amphetamine use and symptoms

The prevalence of specific psychiatric symptoms in past-year and former amphetamine users are shown in Table 2. In those with affective psychotic disorders, there were no statistically significant differences in the unadjusted prevalence rates of symptoms between past-year and former amphetamine users (OR = 0.818–1.71; $p = 0.018$–0.971). Past-year use was associated marginally higher likelihood of reporting several disorganised symptoms, including inappropriate social behaviour ($p = 0.018$; OR = 1.89), racing thoughts ($p = 0.069$; OR = 1.59), reckless activity ($p = 0.057$; OR = 1.65), and any disorganised symptom ($p = 0.046$; OR = 1.71).

Confounding factors included age, employment status, lifetime diagnosis of cannabis dependence/abuse, duration of psychotic disorder, frequent alcohol use, cannabis use, and other illicit substance use (any use of heroin, tranquilisers, cocaine, hallucinogens or ecstasy within the past 12 months). These confounders, as well as antipsychotic medication use and mood stabiliser medication use were adjusted for in subsequent regression analyses (Table 3).

After adjusting for confounding variables, past-year – relative to former – amphetamine users with schizophrenia were more likely to experience hallucinations in at least one sensory modality ($p = 0.056$). Among those with schizophrenia, the odds of experiencing persecutory delusions was more than two-times higher in past-year – relative to former – amphetamine users; however, other delusions were not significantly associated with amphetamine use for this group. Past-year amphetamine users with schizophrenia were more likely to report

Table 1
Demographic characteristics and substance use for past-year versus former amphetamine users.

Amphetamine use group:	Former use ($n = 431$) % (n)	Past-year use ($n = 205$) % (n)	Test values
Age in years, M (SD)	35.0 (0.43)	32.7 (0.56)	$t = 3.17$; $p = 0.002$*
Male sex	66.1 (285)	70.2 (144)	$\chi^2 = 1.07$; $p = 0.300$
Single, never married	66.8 (288)	69.8 (143)	$\chi^2 = 2.74$; $p = 0.253$
Age (years) when left school, M (SD)	16 (0.18)	16 (0.09)	t = 0.47; $p = 0.640$
Paid employment in past 12 months	31.9 (133)	41.5 (85)	$\chi^2 = 6.93$; $p = 0.008$*
Psychotic Disorder			
ICD-10 diagnosis			
Schizophrenia	54.3 (234)	55.1 (113)	$\chi^2 = 0.04$; $p = 0.844$
Affective psychoses	45.7 (197)	44.9 (92)	
Duration of illness in years, M (SD)	14 (9.2)	11 (7.7)	t = 2.99; $p = 0.003$*
Course of illness			$\chi^2 = 3.08$; $p = 0.214$
Single episode with recovery	6.3 (27)	5.4 (11)	
Multiple episode with recovery	66.3 (286)	60.5 (124)	
Continuous chronic illness	27.4 (118)	34.1 (70)	
Substance used in past 12 months			
Mood stabilizers[a]	25.3 (109)	25.4 (52)	$\chi^2 = < 0.001$; $p = 0.984$
Antidepressants[a]	33.6 (145)	27.8 (57)	$\chi^2 = 2.18$; $p = 0.139$
Antipsychotics[a]	84.7 (365)	83.4 (171)	$\chi^2 = 0.16$; $p = 0.680$
Frequent alcohol use[b]	48.7 (210)	63.9 (131)	$\chi^2 = 12.84$; $p = < 0.001$*
Frequent cannabis use[b]	33.8 (143)	64.0 (128)	$\chi^2 = 50.37$; $p = < 0.001$*
Lifetime cannabis abuse/dependence	80.3 (346)	87.3 (179)	$\chi^2 = 4.77$; $p = 0.029$
Other illicit substances[c]	13.7 (59)	52.7 (108)	$\chi^2 = 109.09$; $p = < 0.001$*
Heroin use	11.2 (15)	44.1 (41)	$\chi^2 = 31.96$; $p = < 0.001$*
Tranquiliser use	25.5 (25)	53.2 (33)	$\chi^2 = 12.62$; $p = < 0.001$*
Cocaine use	6.1 (7)	29.1 (23)	$\chi^2 = 18.76$; $p = < 0.001$*
Hallucinogen use	5.4 (12)	22.1 (25)	$\chi^2 = 21.15$; $p = < 0.001$*
Ecstasy use	6.3 (13)	35.9 (47)	$\chi^2 = 47.83$; $p = < 0.001$*

Note. Asterisks (*) indicate statistically significant difference ($p = < 0.05$). Separate baseline characteristics for the schizophrenia and affective psychoses groups are available in Supplementary Table 2.

[a] Prescription medication, further information available in Supplementary Table 3.

[b] Frequent use is defined as at least once per month during past 12 months;

[c] Any use of heroin, tranquilisers, cocaine, hallucinogens or ecstasy during past 12 months.

Table 2
Psychiatric symptom prevalence in former versus past-year amphetamine users in Past 12 months.

	Schizophrenia, % (*n*)				Affective psychotic disorders, % (*n*)			
	Former use (*n* = 234)	Past-year use (*n* = 113)	Total (*n* = 347)	*P* value	Former users (*n* = 197)	Past-year users (*n* = 92)	Total (n = 289)	*P* value
Hallucinations								
Multiple voices	23.5 (55)	35.4 (40)	27.4 (95)	0.020	17.3 (34)	21.7 (20)	18.7 (54)	0.363
Running commentary	26.5 (62)	30.1 (34)	27.6 (96)	0.483	21.8 (43)	29.3 (27)	24.2 (70)	0.164
Non-verbal sounds	24.8 (58)	33.6 (38)	27.7 (96)	0.084	27.4 (54)	23.9 (22)	26.3 (76)	0.529
At least one sensory modality	61.5 (144)	77.0 (87)	66.6 (231)	0.004 *	53.3 (105)	57.6 (53)	54.7 (158)	0.493
Delusions								
Persecutory	50.4 (188)	68.1 (77)	56.2 (195)	0.002 *	48.7 (96)	53.3 (49)	50.2 (145)	0.473
Control	13.6 (32)	15.9 (18)	14.4 (50)	0.575	11.7 (23)	10.9 (10)	11.4 (33)	0.841
Reference	35.9 (84)	44.2 (50)	38.6 (134)	0.134	29.4 (58)	35.9 (33)	31.5 (91)	0.273
Grandiosity	29.9 (70)	32.7 (37)	30.8 (107)	0.593	25.9 (51)	31.5 (29)	27.7 (80)	0.319
Bizarre	20.5 (48)	20.3 (23)	20.5 (71)	0.973	13.2 (26)	13.0 (12)	13.1 (38)	0.971
Any delusion	65.8 (154)	77.9 (88)	69.7 (242)	0.022	58.9 (116)	79.6 (64)	62.3 (180)	0.081
Affective symptoms								
Dysphoria	31.2 (73)	46.9 (53)	36.3 (126)	0.004 *	68.5 (135)	75.0 (69)	70.6 (204)	0.261
Suicidal ideation	21.8 (51)	31.9 (36)	25.1 (87)	0.043	41.1 (81)	48.9 (45)	43.6 (126)	0.213
Anhedonia	29.9 (70)	45.1 (51)	34.9 (121)	0.005 *	67.5 (133)	72.8 (67)	69.2 (200)	0.362
Anxiety	47.8 (112)	42.7 (47)	46.2 (159)	0.373	56.1 (110)	65.6 (59)	59.1 (169)	0.132
Elevated mood	5.1 (12)	10.6 (12)	6.9 (24)	0.059	34.5 (68)	43.5 (40)	37.4 (108)	0.142
Any affective symptom	65.0 (152)	69.9 (79)	66.6 (231)	0.359	87.3 (172)	93.5 (86)	89.3 (258)	0.114
Disorganised symptoms								
Thoughts racing	6.8 (16)	15.9 (18)	9.8 (34)	0.008 *	36.6 (72)	47.8 (44)	40.1 (116)	0.068
Distractibility	6.4 (15)	15.9 (18)	9.5 (33)	0.005 *	38.1 (75)	47.8 (44)	41.2 (119)	0.116
Inappropriate social behaviour	3.8 (9)	10.6 (12)	6.0 (21)	0.013 *	25.4 (50)	39.1 (36)	29.8 (86)	0.017
Reckless activity	4.7 (11)	8.0 (9)	5.8 (20)	0.222	27.9 (55)	39.1 (36)	31.5 (91)	0.056
Any disorganised symptom	26.1 (61)	34.5 (39)	28.8 (100)	0.104	46.2 (91)	60.9 (56)	50.1 (147)	0.020

Note. Asterisks (*) indicate statistically significant difference ($p = < 0.01$) in prevalence of psychiatric symptoms between former and past-year amphetamine users. Unadjusted values available in Supplementary Table 4.

Table 3
Logistic regression for relationship between amphetamine use status and psychiatric symptoms.

	Unadjusted univariate			Adjusted[a] univariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Schizophrenia						
Any hallucination	2.09	1.25–3.48	0.005	1.76	0.98–3.16	0.056
Persecutory delusions	2.10	1.31–3.36	0.002	2.14	.614–2.71	0.006
Dysphoria	1.94	1.22–3.09	0.005	2.12	1.24–3.62	0.006
Anhedonia	1.92	1.21–3.06	0.006	2.01	1.18–3.42	0.010
Thoughts racing	2.58	1.26–5.27	0.009	2.45	1.05–5.69	0.038

Note. [a] Adjusted for age, employment status, alcohol, cannabis and other substance use (including heroin, tranquilisers, cocaine, hallucinogens or ecstasy), duration of illness, antipsychotic and mood stabilising medication use and lifetime cannabis abuse/dependence.

Table 4
Logistic regression for relationship between symptom categories and amphetamine use.

	Unadjusted univariate			Adjusted[a] univariate		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Schizophrenia						
Any hallucination	2.09	1.25–3.48	0.005	2.01	1.14–3.52	0.015
Any delusion	1.82	1.08–3.07	0.023	1.70	0.95–3.03	0.071
Any affective symptom	1.25	0.77–2.03	0.360	1.52	0.89–2.62	0.125
Any disorganised symptom	1.49	0.92–2.42	0.104	1.31	0.76–2.28	0.331
Affective Psychoses						
Any hallucination	1.19	0.72–1.96	0.493	.756	0.63–1.89	0.756
Any delusion	1.59	0.94–2.70	0.082	1.75	0.97–3.18	0.062
Any affective symptom	2.08	0.82–5.26	0.121	2.30	0.81–6.53	0.118
Any disorganised symptom	1.81	1.01–2.99	0.021	1.58	0.89–2.83	0.119

Note. [a] Adjusted for age, employment status, alcohol, cannabis and other substance use (any use of heroin, tranquilisers, cocaine, hallucinogens or ecstasy within the past 12 months), duration of illness, antipsychotic and mood stabilising medication use and lifetime cannabis abuse/dependence.

racing thoughts compared to former users. The odds of experiencing dysphoria and anhedonia two times higher for past-year – relative to former – amphetamine users with schizophrenia. Unadjusted and adjusted values for composite symptom scores are available in Table 4.

4. Discussion

The current study is the first directly examine the relationship between specific psychiatric symptoms and illicit amphetamine use in a community sample of individuals with schizophrenia and affective psychotic disorders. This relationship was explored using validated diagnostic tools and psychopathology measures in a representative community sample of Australians with psychotic disorders (Morgan et al., 2012). The association between past-year illicit amphetamine use and prevalence of specific symptoms of psychosis varied for those diagnosed with schizophrenia and affective psychotic disorders. Consonant with our expectations, past-year amphetamine use in those with schizophrenia was associated with a higher prevalence of hallucinations and persecutory delusions, as well as symptoms of depression (dysphoria and anhedonia) and racing thoughts. Contrary to expectations, however, amphetamine use was unrelated to the profile of psychiatric symptoms in persons with affective psychotic disorders. This apparent lack of equivalent association indicates that amphetamine may be acting on schizophrenia-specific dysfunctions to worsen psychiatric symptoms.

4.1. Schizophrenia

The current study aligns with previous research indicating that illicit amphetamine use can precipitate and exacerbate positive schizophrenic symptoms (Curran et al., 2004), which likely occur through activating dopaminergic pathways in those with schizophrenia. The dopamine hypothesis of schizophrenia holds that overactivity of dopaminergic neurotransmission in mesolimbic pathways results in positive psychotic symptoms of schizophrenia (Maia and Frank, 2017). Amphetamine use also induces the release of dopamine and can result in dopaminergic sensitization in chronic users (Laruelle, 2000; Wang et al., 2010); this occurs when excessive stimulation of the dopamine system increases hyper-reactivity to further pharmacological or environmental dopaminergic triggers. This positive feedback mechanism prompts cumulative dopamine dysfunction in individuals with schizophrenia. Higher rates of racing thoughts in past-year users may be attributable to the direct acute effects of amphetamine intoxication, which are widely observed in individuals without a history of psychotic disorders (Angrist and Gershon, 1970; Courtney and Ray, 2014).

Our findings replicate previous case-control research demonstrating that amphetamine use is related to depression in persons with schizophrenia. Depressive symptoms are reported in up to 75% of persons with schizophrenia, leading some to argue that depression is intrinsic in the expression of schizophrenia and may have a direct role in the formation and maintenance of positive psychotic symptoms (Hartley et al., 2013). Illicit amphetamine use may function as a stressor in activating this underlying predisposition towards depression. Alternatively, depressive symptoms precede and promote amphetamine use. The 'alleviation of dysphoria model' (Dixon et al., 1991) suggests that patients whose symptoms lead to distress or depression attempt to self-medicate with illicit substances. Patients with schizophrenia who experienced worsened positive symptoms may have used amphetamine to mask subsequent dysphoria and improve negative mood. Effective management of depressive symptoms may reduce amphetamine use in those who use substances to alleviate such symptoms.

4.2. Affective psychotic disorders

The current findings conflict with those of Viktorin et al. (2017) who identified an association between prescription methylphenidate and higher risk of mania in those with bipolar disorder. Unlike sustained frequent use associated with prescription medication regimes, two-thirds of the past-year sample within the current study used amphetamine on a recreational (less-than-monthly) basis in an unknown dosage and route of administration. Consistent with our hypothesis, the prevalence of several specific disorganised symptoms which characterise mania within the ICD-10 classification (e.g. reckless activity, inappropriate social behaviour, and racing thoughts) appeared to be higher among past-year – relative to former – amphetamine users with affective psychoses (OR = 1.59–1.89). These differences of small effect size were not considered statistically significant with the use of a stringent alpha value. The current analyses may have lacked sufficient statistical power to detect these differences, which may be identified when comparing symptoms across a larger sample of frequent amphetamine users.

4.3. Clinical implications

The potential for illicit amphetamine use to worsen symptomatology in those with schizophrenia is particularly concerning given the lifetime prevalence rates of stimulant use disorders is 13% in this population (Sara et al., 2015). A higher likelihood of positive psychotic and depressive symptoms may underlie the poorer treatment response, higher rates of non-compliance and overall worse prognosis observed in dual diagnosis patients with both psychotic and amphetamine use disorders (Bartels et al., 1993; Lambert et al., 2005; de Haan et al., 2007). Amphetamine use was associated with delusions and hallucinations despite high rates of past-year antipsychotic medication use (83%) in the current sample. Although this does not reflect the rate of medication adherence, these findings align with evidence that amphetamine use may undermine the efficacy of some antipsychotic treatments (Curran et al., 2004). Clinicians should screen routinely for substance use, especially in the context of non-responsiveness to antipsychotic treatment.

Although we found no evidence for worsened psychiatric symptoms among past-year – relative to former – amphetamine users with affective psychotic disorders, frequent amphetamine use is nonetheless associated with serious impairments in physical and cognitive health, social functioning and financial stability (Darke et al., 2008). Identifying illicit amphetamine use in affective psychotic disorders may be particularly challenging given the similarity in symptom profiles between users and non-users.

Dual diagnosis patients with schizophrenia should be informed about how symptoms may be exacerbated or precipitated by amphetamine use. Whilst depressive symptoms appear to be a prominent element in the relationship between schizophrenia and amphetamine use, clinicians often focus exclusively on positive psychotic symptoms and infrequently offer treatment for affective symptoms (Cosoff and Hafner, 1998). Illicit amphetamine use often occurs with high rates of illicit polysubstance use (Darke and Hall, 1995; McKetin et al., 2005). As such, clinicians must be particularly cautious about potential interactions across multiple substances when prescribing antidepressant and antipsychotic medication. Clozapine appears effective in reducing both positive psychotic symptoms and stimulant use in those with schizophrenia (Lubman et al., 2010) and could be integrated with motivational interviewing or cognitive behavioural therapy to also address depression in dual diagnosis patients.

4.4. Limitations and future research

Several key limitations must be addressed. First, there are likely other unmeasured confounding factors which may be associated with both amphetamine use and psychiatric symptoms, such as a familial risk of psychotic illness (Chen et al., 2005) and the amphetamine dosage and route of administration (Matsumoto et al., 2002). Second, although previous research suggests amphetamine use exacerbates psychotic symptoms (Curran et al., 2004), it is also plausible that psychotic symptoms promote amphetamine use. We were unable to examine the precise dose-relationship between psychiatric symptoms and amphetamine use as too few participants reported amphetamine use on a daily, weekly or monthly basis. Future replications may establish the direction of the observed correlations through longitudinal monitoring of amphetamine use and changes in symptom prevalence and severity. Third, certain neurotoxic effects of amphetamine may persist beyond 12 months after use (Yui et al., 1999). As the specific duration of abstinence is unknown in the former user group, these neurobiological characteristics may persist and underlie some psychiatric symptomatology. Future research should employ a comparison group of individuals with no history of amphetamine use. Finally, the reliability of self-reported drug use behaviours and past-year psychiatric symptoms may have been impacted by recall bias. To reduce recall inaccuracy, the DIP measure of psychiatric symptoms incorporates information obtained from discharge summaries, case notes, case managers, or other service staff, where available. Similarly, confidential self-report measures of drug use behaviour have been shown to be reliable and valid when compared to biomarkers, criminal records and collateral interviews (Darke, 1998).

There are further caveats to the generalisability of these results. Two-thirds of participants used amphetamine on a less-than-monthly basis. Our findings therefore may not reflect psychiatric symptoms in persons with heavy, frequent and dependent amphetamine use. Differences in symptoms between frequent current amphetamine users

and former users would likely be more pronounced than identified in the current study. Similarly, in recruiting participants through community mental health services, these results are may not generalise to people with a psychotic illness who have not been in contact with any public or private mental health services, nor those who are treated by private practitioners.

4.5. Conclusion

Amphetamine use is associated with higher rates of specific psychiatric symptoms in those with schizophrenia, however, this relationship is less clear for those with affective psychotic disorders. Further research is needed to confirm the underlying mechanisms and directions of these associations. Dual diagnosis patients should be provided with integrated treatment for psychotic symptoms, depression and substance abuse to ultimately improve wellbeing and prognosis.

Acknowledgements

This publication is based on data collected in the framework of the 2010 Australian National Survey of High Impact Psychosis (SHIP). The members of the SHIP Study Group at the time were: V. Morgan (National Project Director), A. Jablensky (Chief Scientific Advisor), A. Waterreus (National Project Coordinator), R. Bush, V. Carr, D. Castle, M. Cohen, C. Galletly, C. Harvey, B. Hocking, A. Mackinnon, P. McGorry, J. McGrath, A. Neil, S. Saw, H. Stain. The main study was funded by the Australian Government Department of Health and Ageing. This paper acknowledges, with thanks, the hundreds of mental health professionals who participated in the preparation and conduct of the survey and the many Australians with psychotic disorders who gave their time and whose responses form the basis of this publication. The authors report no conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.04.015.

References

American Psychiatric Association., 2013. Diagnostic and Statistical Manual of Mental Disorders, 5th ed. American Psychiatric Association, Arlington, VA.
Angrist, B., Gershon., S., 1970. The phenomenology of experimentally induced amphetamine psychosis-preliminary observations. Biol. Psychiatry 2, 95–107.
Bartels, S., Teague, G., Drake, R., Clark, R., Bush, P., Noordsy, D., 1993. Substance abuse in schizophrenia: service utilization and costs. J. Nerv. Ment. Dis. 181, 227–232.
Castle, D., Jablensky, A., McGrath, J., Carr, V., Morgan, V., Waterreus, A., et al., 2006. The diagnostic interview for psychoses (DIP): development, reliability and applications. Psychol. Med. 36, 69–80.
Chen, C., Lin, S., Sham, P., Ball, D., Loh, W., Murray, R., 2005. Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. Am. J. Med. Genet. B. Neuropsychiatr. Genet. 136B, 87–91.
Cosoff, S., Hafner, R., 1998. The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. Aust. N. Z. J. Psychiatry 32, 67–72.
Courtney, K., Ray, L., 2014. Methamphetamine: an update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. Drug Alcohol. Depend. 143, 11–21.
Curran, C., Byrappa, N., McBride, A., 2004. Stimulant psychosis: systematic review. Br. J. Psychiatry 185 196-20.
Darke, S., 1998. Self-report among injecting drug users: a review. Drug Alcohol. Depend. 51, 253–263.
Darke, S., Hall, W., 1995. Levels and correlates of polydrug use among heroin users and regular amphetamine users. Drug Alcohol. Depend. 39, 231–235.
Darke, S., Kaye, S., McKetin, R., Duflou, J., 2008. Major physical and psychological harms of methamphetamine use. Drug Alcohol. Rev. 27, 253–262.
Dixon, L., 1999. Dual diagnosis of substance abuse in schizophrenia: prevalence and impact on outcome. Schizophr. Res. 35, 93–100.
Dixon, M., Haas, G., Weiden, P., Sweeney, J., Frances, A., 1991. Drug abuse in schizophrenic patients: clinical correlates and reasons for use. Am. J. Psychiatry 148, 224–230.
Hartley, S., Barrowclough, C., Haddock, G., 2013. Anxiety and depression in psychosis: a systematic review of associations with positive psychotic symptoms. Acta Psychiatr. Scand. 128, 327–346.
de Haan, L., van Amelsvoort, T., Dingemans, P., Linszen, D., 2007. Risk factors for medication non-adherence in patients with first episode schizophrenia and related disorders; a prospective five year follow-up. Pharmacopsychiatry 40, 264–268.
Hunt, G., Siegfried, N., Morley, K., Sitharthan, T., Cleary, M., 2013. Psychosocial interventions for people with both severe mental illness and substance misuse. Cochrane Libr. 10 CD001088.
Laruelle, M., 2000. The role of endogenous sensitization in the pathophysiology of schizophrenia: implications from recent brain imaging studies. Brain Res. Rev. 31, 371–384.
Lambert, M., Conus, P., Lubman, D., Wade, D., Yuen, H., Moritz, S., et al., 2005. The impact of substance use disorders on clinical outcome in 643 patients with first-episode psychosis. Acta. Psychiatr. Scand. 112, 141–148.
Lubman, D., King, J., Castle, D., 2010. Treating comorbid substance use disorders in schizophrenia. Int. Rev. Psychiatr. 22, 191–201.
Maia, T., Frank, M., 2017. An integrative perspective on the role of dopamine in schizophrenia. Biol. Psychiatry 81, 52–66.
Matsumoto, T., Karmijo, A., Miyakawa, T., Endo, K., Yabana, T., Kishimoto, H., et al., 2002. Methamphetamine in Japan: the consequences of methamphetamine abuse as a function of route of administration. Addiction 97, 809–817.
McKetin, R., Kelly, E., McLaren, J., 2005. The characteristics of treatment provided for amphetamine use in New South Wales, Australia. Drug Alcohol Rev 24, 433–436.
McElroy, S., Altshuler, L., Suppes, T., Keck, P., Frye, M., et al., 2001. Axis I psychiatric comorbidity and its relationship to historical illness variables in 288 patients with bipolar disorder. Am. J. Psychiatry 158, 420–426.
McGuffin, P., Farmer, A., Harvey, I., 1991. A polydiagnostic application of operational criteria in studies of psychotic illness. Development and reliability of the OPCRIT system. Arch. Gen. Psychiatry 48, 764–770.
Morgan, V., Waterreus, A., Jablensky, A., Mackinnon, A., McGrath, J., Carr, V., et al., 2012. People living with psychotic illness in 2010: The second Australian national survey of psychosis. Aust. N. Z. J. Psychiatry 46, 735–752.
Sara, G., Large, M., Matheson, S., Burgess, P., Malhi, G., Whiteford, H., et al., 2015. Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation. Aust. N. Z. J. Psychiatry 49, 106–117.
Schimmelmann, B., Conus, P., Cotton, S., Kupferschmid, S., McGorry, P., Lambert, M., 2012. Prevalence and impact of cannabis use disorders in adolescents with early onset first episode psychosis. Eur. Psychiatry 27, 463–469.
Soyka, M., Albus, M., Immler, B., Kathmann, N., Hippius, H., 2001. Psychopathology in dual diagnosis and non-addicted schizophrenics – are there differences. Eur. Arch. Psychiatry Clin. Neurosci. 251, 232–238.
Stone, J., Fisher, H., Major, B., Chisholm, B., Woolley, J., Lawrence, J., et al., 2014. Cannabis use and first-episode psychosis: relationship with manic and psychotic symptoms, and with age at presentation. Psychol. Med. 44, 499–506.
StataCorp., 2015. Stata Statistical Software: Release 14. StataCorp LP, College Station, TX.
Viktorin, A., Rydén, E., Thase, M., Chang, Z., Lundholm, C., D'Onofrio, et al., 2017. The risk of treatment-emergent mania with methylphenidate in bipolar disorder. Am. J. Psychiatry 174, 341–348.
Wang, M., Pei, L., Fletcher, P., Kapur, S., Seeman, P., Liu, F., 2010. Schizophrenia, amphetamine-induced sensitized state and acute amphetamine exposure all show a common alteration: increased dopamine D2 receptor dimerization. Mol. Brain 3, 25.
Wing, J., Babor, T., Brugha, T., Burke, J., Cooper, J., Giel, R., et al., 1990. SCAN. Schedules for clinical assessment in neuropsychiatry. Arch. Gen. Psychiatry 47, 589–593.
Winokur, G., Turvey, C., Akiskal, H., Coryell, W., Solomon, D., et al., 1998. Alcoholism and drug abuse in three groups—bipolar I, unipolars and their acquaintances. J. Affect. Disord. 50, 81–89.
Weiss, R., Kolodziej, M., Griffin, M., Najavits, L., Jacobson, L., Greenfield, S., 2004. Substance use and perceived symptom improvement among patients with bipolar disorder and substance dependence. J. Affect. Disord. 79, 279–283.
World Health Organisation, 1992. ICD-10 Classification of Mental and Behavioural Disorder: Clinical Descriptions and Diagnostic Guidelines. World Health Organisation, Geneva.
Yui, K., Goto, K., Ikemoto, S., Ishiguro, T., Angrist, B., et al., 1999. Neurobiological basis of relapse prediction in stimulant-induced psychosis and schizophrenia: the role of sensitization. Mol. Psychiatry 4, 512–523.

Study Three: Is there a discrete negative symptom dimension in people who use methamphetamine?

This study has been published as following journal article:
Voce, A., Burns, R., Castle D., Calabria, B., & McKetin, R. (2019). Is there a discrete negative symptom dimension in people who use methamphetamine? *Comprehensive Psychiatry*, 93: 27-32.

Foreword:

Study three addressed the third research question of this thesis: *What is the underlying factor structure of psychiatric symptoms among people who use methamphetamine (and do not have SZ)?* Exploratory factor analysis was used to examine the structure of current (past-month) psychiatric symptoms among people who had use methamphetamine in the past month (n=153), and did not meet DSM-IV criteria for lifetime diagnoses of schizophrenia (SZ). This study was intended to provide a greater understanding of the factor structure of psychiatric symptoms among this population, and provide insight into how this structure could differ from SZ. As particular debate has focused on whether negative symptoms could be a point of distinction between SZ and MAP in clinical settings, this study was specifically used to examine the presence of a negative syndrome and its relationship with methamphetamine use.

Corrections

At the time of thesis submission, there were three errors within the printed version of this paper. First, the number of participants included in this study equals 153 (not 154). Second, there are two instances where the number of participants (*n*) in each latent class was switched with the percentage of participants (%) in each class (in the abstract and section 3.4). To clarify, class one comprised 68 participants (44% of the sample), class two comprised 47 participants (31% of the sample), and class three comprised 38 participants (25% of the sample). Third, the printed version incorrectly states "*The three-factor model reported the lowest BIC value and the two-factor solution reported the lowest AIC value (Supplementary Table 1)*" (section 3.2). The three-factor model had a lower AIC value (7466) than the two-factor model (7550).

A corrigendum was submitted to the journal to amend these errors in January 2021.

Comprehensive Psychiatry 93 (2019) 27–32

Contents lists available at ScienceDirect

Comprehensive Psychiatry

journal homepage: www.elsevier.com/locate/comppsych

Is there a discrete negative symptom syndrome in people who use methamphetamine?

Alexandra Voce [a,*], Richard Burns [a], David Castle [b,c], Bianca Calabria [d,e], Rebecca McKetin [f,e]

[a] Centre for Research on Ageing, Health and Wellbeing, Australian National University, Building 54, Mills Road, Acton, ACT 2601, Australia
[b] St Vincent's Hospital, 41 Victoria Parade, Fitzroy, VIC 3065, Australia
[c] Department of Psychiatry, University of Melbourne, Grattan St, Melbourne, VIC 3010, Australia
[d] National Centre for Epidemiology and Population Health, Australian National University, Building 62, Mills Road, Acton, ACT, 2601, Australia
[e] National Drug and Alcohol Research Centre, University of New South Wales, 22-32 King Street, Randwick, NSW 2031, Australia
[f] National Drug Research Institute, Curtin University, GPO Box 1987, Perth, WA 6845, Australia

ARTICLE INFO

Keywords:
Amphetamine
Methamphetamine-induced psychosis
Psychostimulants
Factor analysis
Negative psychotic symptoms

ABSTRACT

Background: Positive psychotic symptoms have consistently been associated with methamphetamine use but the presence of a negative symptom cluster remains unclear. We used exploratory factor analysis to examine whether a discrete negative syndrome could be delineated among methamphetamine users, and to examine the clinical correlates of this syndrome.

Method: Participants ($N = 154$) were people who used methamphetamine at least monthly and did not meet DSM-IV diagnostic criteria for lifetime schizophrenia. Scores on the Brief Psychiatric Rating Scale for the past month were subject to exploratory factor analysis. Latent class analysis was applied to resultant factor scores to determine whether negative and positive factors were experienced by the same participants. Past-month substance use measures were days of use for each drug type and methamphetamine dependence assessed using the Severity of Dependence Scale.

Results: We articulated a three-factor model including 'positive/activation symptoms' (e.g. suspiciousness, hallucinations, conceptual disorganisation, tension), 'affective symptoms' (e.g. depression, anxiety) and 'negative symptoms' (e.g. blunted affect, motor retardation). Positive-activation and affective symptoms (but not negative symptoms) were positively correlated with past month days of methamphetamine use ($r = 0.16$; $r = 0.25$) and severity of dependence ($r = 0.24$; $r = 0.41$). Negative symptoms were correlated with heroin ($r = 0.24$) and benzodiazepine use ($r = 0.21$). Latent class analysis revealed a three-class model comprising a positive-symptom class (44%, high positive-activation, low negative symptoms), a negative-symptom class (31%, low positive-activation, high negative symptoms), and a low-symptom class (38%, low on all factors).

Conclusions: A negative symptom syndrome exists among people who use methamphetamine, but this appears related to polysubstance use rather than forming a part of the psychotic syndrome associated with methamphetamine use. Overlooking the role of polysubstance use on negative symptoms may conflate the profiles of methamphetamine-associated psychosis and schizophrenia.

1. Introduction

Differentiating between schizophrenia and substance-induced psychosis in methamphetamine users is notoriously difficult [1], and previous researchers have argued that these two disorders manifest a common symptom profile [2]. Robust evidence exists for a positive psychotic syndrome (i.e. delusions and hallucinations) precipitated by acute methamphetamine exposure in people without schizophrenia [1,3–8], and the presence of these positive symptoms are core diagnostic features for both substance-induced psychosis and schizophrenia (diagnostic and statistical manual for mental disorders fifth edition; DSM-V [9]). However, unlike for schizophrenia, the diagnostic criteria for substance-induced psychosis does not include negative psychotic symptoms, which are characterised by absences or reductions in movement, speech, affect and motivation (i.e. poverty of speech, psychomotor retardation, and flattened or incongruous affect). The absence of negative symptoms in the methamphetamine-associated psychosis

* Corresponding author at: Centre for Research on Ageing, Health and Wellbeing, Australian National University, Room 1.16, Building 54, Mills Road, Florey, ACT 2601, Australia.
E-mail addresses: alexandra.voce@anu.edu.au (A. Voce), richard.burns@anu.edu.au (R. Burns), David.CASTLE@svha.org.au (D. Castle), bianca.calabria@anu.edu.au (B. Calabria), rebecca.mcketin@curtin.edu.au (R. McKetin).

https://doi.org/10.1016/j.comppsych.2019.06.002

may be a potentially crucial point of distinction from schizophrenia. However, the literature has been mixed regarding the relationship between methamphetamine use and negative psychotic symptoms.

A recent systematic review [7] found that <20% of studies examining the symptom profile of methamphetamine-associated psychosis report negative symptoms. In the studies that do report negative symptoms, the prevalence rate is typically 20% - 26% of patients [8,10]. However, McKetin et al. [6] examined psychiatric symptom exacerbation associated with methamphetamine use and found no evidence for a negative psychotic syndrome. This suggests that negative symptoms are not acutely precipitated by methamphetamine use but may instead result from various confounding factors occurring in this population. This may include the primary or secondary effects of other substances, notably antipsychotic medication use [11], or methamphetamine-related depression which can manifest as affective blunting and social withdrawal [12]. These hypotheses have not been tested empirically in the methamphetamine user population.

A lack of association between acute methamphetamine use and negative symptoms is supported by the schizophrenia literature. A systematic review of 32 experimental studies involving the administration of psychostimulants in people with schizophrenia indicated that whilst positive symptoms increased in 30–70% of patients, negative symptoms typically decreased or remained stable [13]. Accordingly, neurobiological studies of schizophrenia indicate increased dopamine in the striatum occurs with the emergence of positive symptoms, whereas negative symptoms have been associated with reductions in dopamine, particularly in mesocortical tracts [14,15]. Although this research focuses on individuals with schizophrenia, it suggests that the surge of dopamine released during acute methamphetamine exposure would likely result in a symptom profile characterised by positive – rather than negative – psychotic symptoms.

The current study aimed to determine whether a discrete negative symptom syndrome exists in the psychiatric profile of methamphetamine users who did not meet diagnostic criteria for schizophrenia, and to understand how this syndrome relates to methamphetamine use. Exploratory factor analysis of current psychiatric symptoms was used to identify whether a negative symptom syndrome exists in this population. We then examined whether the derived factors were associated with measures of methamphetamine and other substance use, familial morbidity for psychotic disorders, and other sociodemographic risk factors for psychosis (e.g., younger age, male gender, and immigration). Latent class analysis was then used to identify subgroups of participants based on their scores across the derived factors. We hypothesised that if negative symptoms are part of an acute methamphetamine-associated psychosis syndrome then we would expect that same group of people who experience negative symptoms would also experience positive psychotic symptoms, and that these syndromes would both be correlated with methamphetamine use.

2. Method

2.1. Procedure

Participants were recruited in Canberra, Australia, through word-of-mouth, online and print media advertisements, and flyers placed at needle and syringe programs and on public notice boards. Inclusion criteria were use of methamphetamine on at least six occasions over the past 6 months and being at least 18 years of age. To measure typical patterns of substance use in the past month, participants were excluded if they had been incarcerated, hospitalised or in residential drug treatment during the month prior to interview. All participants were volunteers who provided informed consent and were reimbursed AU$40 for their time and travel expenses. Interviews were one-hour in duration and were conducted in public locations convenient to the participant (e.g., cafes, shopping malls). The study was approved by the Australian National University's Human Research Ethics Committee.

Participants were excluded from analyses if they (i) had not used methamphetamine in the past month ($n = 10$), (ii) met the DSM-IV diagnostic criteria for lifetime schizophrenia ($n = 20$) assessed using the Composite International Diagnostic Interview (CIDI [16]), or (iii) had missing data on the Brief Psychiatric Rating Scale (BPRS [17]) or the CIDI ($n = 6$). The CIDI module did not measure negative and disorganised symptoms (DSM-V criteria A3-A5 for schizophrenia), and did not screen for bipolar disorder or schizoaffective disorder (DSM-V criteria D for schizophrenia).

2.2. Measures

2.2.1. Psychiatric symptoms

Psychiatric symptoms in the past month were assessed using the BPRS, in which symptom severity is rated from (1) “not present” to (7) “extremely severe” [17]. A selection of interviews was audiotaped, with consent the participants ($n = 21$), and rated by a second interviewer (R.M) to calculate interrater reliability. Cohen's kappa values were at an acceptable level for all symptoms other than elevated mood and bizarre behaviour (< 0.40) [18], and therefore these items were excluded from analyses. After excluding elevated mood and bizarre behaviour, interrater agreement for categorical ratings of psychiatric symptoms was substantial (kappa = 0.69, range = 0.44–0.90).

2.2.2. Substance use and other measures

Self-reported days of use in the past four weeks was assessed for methamphetamine, alcohol, tobacco, heroin, other opioids, cocaine, ecstasy, cannabis, other hallucinogens, inhalants, benzodiazepines, antidepressants, and antipsychotic medication (“How many days have you used [substance] in the past month?”). Other measures of methamphetamine use included age of first use and dependence in the past month. Dependence was defined as a score of 4 or greater on the Severity of Dependence Scale (SDS [19]), which yields 71% sensitivity and 77% specificity against a DSM-IV diagnosis of severe amphetamine dependence [20]. Demographic measures included age in years, sex, years of education, employment status, and current living arrangement. Family history of psychiatric illness was measured using adapted modules from the Diagnostic Interview for Psychosis (DIP [21]).

2.3. Statistical analyses

Factor analysis and latent class analysis were conducted in MPlus version 7.2 [22]. Exploratory factor analysis was used to examine current psychiatric symptoms and their inter-correlations, and was estimated with the principal axis factors method and an oblique oblimin rotation. Only factor loadings of 0.32 or higher were considered [23] as this reflects 10% of the variance accounted for by the latent factor. Factor analysis models with increasing numbers of extracted latent factors were compared with a series of goodness of fit indicators, including Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), with lower values reflecting a better fitting model. Once the optimal number of latent factor dimensions to be extracted were identified, latent class analysis was applied to the extracted factor scores for each participant.

The five-class mixture model could not be estimated with 1000 random starts, and thus, indices of model fit were compared across two-class, three-class and four-class models. The best-fitting model was selected based on higher entropy, lower AIC and BIC. The Vuong-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR LRT) and the parametric bootstrapped likelihood ratio test (BLRT) were used to examine whether each additional class significantly improved the fit of the model to the data [24,25]. Descriptive analyses were undertaken in Stata version 14.1 [26], with medians (*mdn*) reported for skewed data. Comparisons of median factor scores between each class were conducted with Wilcoxon rank-sum test, with an alpha value of $p < .01$ used to adjust for multiple testing. Two-way independent samples *t*-

tests (or Wilcoxon rank-sum test for skewed data) was used to compare factors between sample subgroups ($p < .05$ considered statistically significant). Correlates between factor scores and continuous variables (i.e. age) were examined using Pearson's pairwise correlations for normally distributed data (or Spearman's rank correlation for skewed continuous data).

3. Results

3.1. Sample characteristics

The sample consisted of 154 participants, with a median age of 39.4 years (SD = 10.1). The majority were male (69%), unemployed (67%) and single (64%). The median age of first methamphetamine use was 19.3 years (SD = 7.1) and participants had used for a median of 20.1 years (SD = 9.5). The highest endorsements for primary route of methamphetamine administration in the past month were for injection (74%) and for smoking (20%). Participants had used methamphetamine on a median of 11.5 days (interquartile range = 5–20) in the past month, and 42% were dependent on methamphetamine. Participants had used a median of 5 different drug classes (IQR = 4–6) in the past month, most commonly tobacco (98%), cannabis (79%), alcohol (65%), benzodiazepines (51%), and heroin (48%). The most prevalent BPRS symptoms included anxiety (71%), depression (64%), hostility (52%), suspiciousness (36%), and self-neglect (34%), while relatively few participants reported disorientation (1%), motor retardation (1%), mannerisms and posturing (2%), or uncooperativeness (2%).

3.2. Exploratory factor analysis

Indices of model fit were compared across one-, two-, three-, four- and five-factor models for the 22 BPRS items. The three-factor model reported the lowest BIC value and the two-factor solution reported the lowest AIC value (Supplementary Table 1). The three-factor model was selected as the most parsimonious factor model with the highest factor loadings (Table 1). Disorientation, self-neglect and uncooperativeness demonstrated poor discrimination between the factors and were excluded from the final three-factor solution. Disorientation failed to significantly load on any factor, self-neglect cross-loaded across factor two (0.59) and three (0.75); and uncooperativeness loaded moderately first (0.59) and the second factor (0.64).

The first identified factor encompassed grandiosity, unusual thought content, hallucinations, tension, conceptual disorganisation, hyperactivity, distractibility, excitement, and mannerisms (labelled 'positive/activation symptoms'). A second 'affective symptoms' factor comprised of depression, anxiety, suicidality, guilt, somatic concern, and hostility. The third 'negative symptoms' factor was characterised by blunted affect, emotional withdrawal, and motor retardation. Internal reliability for each factor ($\alpha = 0.73–0.78$) was at an acceptable level (Cortina, 1993). Positive-activation symptoms shared a moderate positive correlation with the affective symptoms ($r = 0.41$, $p \leq 0.001$), and a large negative correlation with negative symptoms ($r = -0.63$, $p \leq 0.001$). There was no statistically significant correlation between negative and affective symptoms ($r = 0.04$, $p = .591$). Inter-item correlations for each factor are provided in Supplementary Tables 2–4.

Table 1
Exploratory factor analysis results.

	Factor 1: Positive/activation	Factor 2: Affect	Factor 3: Negative	Unadjusted median (interquartile range)[a]
Factor correlations, *r* (*p*-value)				
Positive/activation	–	0.410 (<0.001)	−0.630 (<0.001)	–
Affect	–	–	0.044 (0.591)	–
Item loadings				
Grandiosity	0.995			1.0 (1–1)
Distractibility	0.987			1.0 (1–1)
Unusual thought con.	0.980	0.455		2.0 (1–3)
Suspiciousness	0.918	0.653		2.0 (1–4)
Hallucinations	0.889	0.689		2.0 (1–3)
Mannerisms	0.861	0.449		1.0 (1–1)
Conceptual disorg.	0.775			1.0 (1–1)
Tension	0.415			1.0 (1–2)
Excitement	0.412			1.0 (1–1)
Hyperactivity	0.395			1.0 (1–1)
Suicidality		0.998		2.0 (1–4)
Anxiety		0.996		4.0 (2–5)
Depression		0.995		4.0 (3–5)
Guilt		0.979		1.0 (1–3)
Somatic concern		0.953		2.0 (1–2.5)
Hostility		0.951		3.0 (2–5)
Blunted affect			0.995	1.0 (1–2)
Motor retardation			0.993	1.0 (1–1)
Emotional with.			0.989	1.0 (1–2)
Disorientation				1.0 (1–1)
Self-neglect		0.586	0.749	2.0 (1–4)
Uncooperativeness	0.640		0.595	1.0 (1–2)
Alpha reliability	0.79	0.73	0.77	–
Explained variance[b]	0.35	0.25	0.21	–

Note. Factor loadings below 0.30 have been suppressed. Unusual thought con. = Unusual thought content. Conceptual disorg. = Conceptual disorganisation. Emotional with. = Emotional withdrawal.
[a] Median (IQR) for item across total sample.
[b] Cumulative explained variance = 0.81.

3.3. Correlations between factors and substance use

Correlates of each factor are shown in Table 2. Scores on both the positive-activation and affective symptom dimensions were positively correlated with median days of methamphetamine use in the past month, as well as with median dependence score and median days of antipsychotic medication use (Table 2). Participants with a familial history of affective disorder scored higher on positive-activation symptoms and affective symptoms. Negative symptoms were positively correlated with days of heroin use and days of benzodiazepine use in the past month. Affective symptoms were positively correlated with a median of drug classes used in the past month. Unemployed participants scored higher on the positive-activation symptoms, and female participants scored higher on affect.

3.4. Latent class analysis

LCA was applied to factor scores to identify classes of participants who had similar scores across the positive-activation, affective and negative symptoms. Indices of model fit (BIC and AIC) across two, three and four-class models were compared. Likelihood ratio tests indicated that goodness-of-fit was significantly improved with each successive model (Table 3). Relative to the three-class model, the four-class model included a very small fourth class ($n = 9$) which shared a largely overlapping symptom profile with the third class. The most parsimonious model was the three-class model (Fig. 1, Supplementary Table 4), with adequate entropy (0.785) and low BIC/AIC. Class one (44%, $n = 68$) is referred to as the positive-symptom class and reported high positive-activation symptoms compared to class two ($p \leq 0.001$) and three ($p \leq 0.001$). Class two (31%, $n = 47$), referred to as the negative-symptom class, reported comparatively higher negative symptoms factor scores compared to class one ($p \leq 0.001$) and three ($p \leq 0.001$). Class three (38%, $n = 25$) reported low scores on all three factors, and is thus referred to as the low-symptom class (Fig. 1, Supplementary Table 4). All three classes had similar affective symptom scores. Participants in the negative-symptom class reported significantly more days of benzodiazepine use ($z = -2.32$, $p = .020$, *mdn* difference = 15.5 days), and

Table 2
Sociodemographic, drug use and psychiatric correlates of factor dimensions.

	Positive-activation	Affect	Negative
Spearman's rank correlation (*p* value)			
Age in years	0.01 (0.931)	−0.04 (0.593)	0.023 (0.777)
Years of education	−0.01 (0.861)	−0.01 (0.903)	0.004 (0.960)
Age of first methamphetamine use	−1.57 (0.119)	−1.54 (0.126)	0.86 (0.389)
Years of methamphetamine use	0.07 (0.366)	−0.01 (0.948)	−0.02 (0.756)
Wilcoxon rank-sum test value (*p* value)			
Male sex	1.20 (0.231)	2.31 (0.022)*	−0.64 (0.518)
Currently unemployed	2.12 (0.035)*	1.18 (0.238)	0.24 (0.806)
Single and never married	−0.44 (0.656)	−0.13 (0.893)	0.17 (0.862)
Immigrant background	0.36 (0.717)	0.98 (0.325)	0.01 (0.993)
Family history of affective disorder	1.97 (0.050)*	3.29 (0.001)*	1.24 (0.217)
Family history of schizophrenia	−1.57 (0.119)	−1.54 (0.126)	0.86 (0.389)
Substance use in past month, *r* (*p*-value)			
Median SDS score	0.24 (0.003)*	0.41 (<0.001)*	−0.05 (0.531)
Days of methamphetamine use	0.16 (0.043)*	0.25 (0.002)*	0.001 (0.995)
Days of heroin use	−0.30 (0.004)*	−0.03 (0.753)	0.24 (0.019)*
Days of other opioid use[a]	−0.10 (0.408)	−0.08 (0.493)	−0.15 (0.189)*
Days of benzodiazepines use	−0.13 (0.200)	0.114 (0.270)	0.213 (0.037)*
Days of alcohol use	−0.10 (0.328)	0.11 (0.249)	0.14 (0.135)
Days of cannabis use	−0.03 (0.699)	0.02 (0.860)	0.03 (0.714)
Days of antipsychotic use	0.18 (0.031)*	0.15 (0.059)	0.02 (0.772)
Days of antidepressant use	−0.14 (0.338)	−0.06 (0.689)	0.229 (0.118)
Median number of drug classes used[b]	0.02 (0.756)	0.25 (0.002)*	0.08 (0.314)

[a] Other opioids includes methadone, morphine, and prescription pain killers.
[b] Drug classes includes methamphetamine, alcohol, tobacco, heroin, other opioids, cocaine, ecstasy, cannabis, other hallucinogens, inhalants, benzodiazepines, antidepressants, and antipsychotic medication.
* $p < .05$.

marginally more days of heroin use ($z = -1.73$, $p = .084$, *mdn* difference = 7.0 days) in the past month compared to the positive-symptom class. These two classes did not differ on days of methamphetamine use in the past month ($z = -0.661$, $p = .508$, *mdn* difference = 2.0 days). A supplementary three-class latent model was conducted on the original 22 BPRS items (Table S6; Fig. S1).

Table 3
Criterion for model selection in latent class analysis.

	Two-class	Three-class	Four-class
Entropy	0.869	0.785	0.817
AIC/Adjusted BIC	1180/1179	1144/1142	1119/1117
BLRT (*p-value*)	−614.8 (<0.001)	−580.1 (<0.001)	−558.2 (<0.001)
VLMR LRT (*p-value*)	−614.8 (0.044)	−580.1 (0.031)	−558.2 (0.0202)

Note. AIC = Akaike Information Criterion, BIC = Bayesian Information Criterion, BLRT = parametric bootstrapped likelihood ratio test, VLMR LRT = Vuong-Lo-Mendell-Rubin Likelihood Ratio Test.

4. Discussion

We identified a negative symptom syndrome in methamphetamine users without a diagnosis of schizophrenia, which unlike the positive-activation or affective symptoms, was not correlated with current methamphetamine use or related to familial risk for psychosis. These results suggest that negative symptoms are unlikely to be due to the direct effect of acute methamphetamine use. In addition, negative symptoms were reported by a subpopulation of methamphetamine users which differed from the subgroup of participants who experienced positive psychotic symptoms. This suggests that negative symptoms are not occurring within the same syndrome as methamphetamine-associated psychosis. The negative syndrome was not correlated with methamphetamine-related depression (i.e. the affect factor), nor was it related to the secondary side effects of antipsychotic medication. Several alternative explanations are considered below.

Negative symptoms may be a consequence of neurotoxic impairment in long-term methamphetamine users. Prolonged or heavy methamphetamine use impacts normal brain function and prompts changes in brain structure [27,28], which in turn, may indirectly precipitate negative symptoms [14]. Longitudinal evidence into methamphetamine users indicates that negative symptoms become increasingly prominent as positive symptoms subside over time [29,30]. This 'residual state' is observed in other psychotic disorders [31]. This explanation is not reflected in the current findings because negative symptoms were not associated with duration of methamphetamine use (in years) or frequency of methamphetamine use. Nonetheless, it would be informative for future longitudinal studies to assess whether these psychiatric factors alternate or interact over time, and whether negative symptoms may have prognostic utility in predicting clinical course and treatment response [32–34].

Alternatively, negative symptoms in the current sample may reflect a pre-existing neurobiological or genetic vulnerability found in some individuals, and these symptoms are antecedent to – rather than induced by – methamphetamine use. Although not tested directly, the self-medication hypothesis [35] suggests that people with premorbid negative symptoms [36] may subsequently use substances (such as methamphetamine) to temporarily alleviate the distress and suffering associated with these symptoms. People with negative symptoms may use methamphetamine to increase sociability and reduce blunted affect, and indeed, amphetamine does appear to obscure negative symptoms in experimental studies of schizophrenia [13]. A self-medication approach does not explain why individuals in the negative-symptoms class do not report positive symptoms. We would expect to these individuals to either report positive symptoms alone, with negative symptoms masked by methamphetamine use, or to manifest both negative and positive symptoms which vary based on fluctuating patterns of methamphetamine use over the past month.

Finally, negative symptoms measured in this study may be an artefact of polysubstance use. The current study found that the negative syndrome was positively correlated with days of heroin use and days of benzodiazepine use in the past month. Heroin and benzodiazepine use was common among the current sample, and this polysubstance use pattern is common among people who inject drugs [37]. In contrast to the psychostimulant effects of methamphetamine, heroin and benzodiazepines are central nervous system depressants which produce reduced neurophysiological processing, impaired motor movements, and respiratory and cardiovascular depression [38]. The intoxication effects of these depressant drugs correspond to the observed negative symptoms in the current study, including slowed movements and speech, social withdrawal, and blunted emotional expressiveness [39–41]. Our results align with a recent Canadian study of polysubstance users [42], in which frequency of opioid use was associated with emotional withdrawal, social withdrawal, and motor retardation, but was not associated with measures of positive psychotic symptoms. Likewise, the current study found that frequency of methamphetamine use was

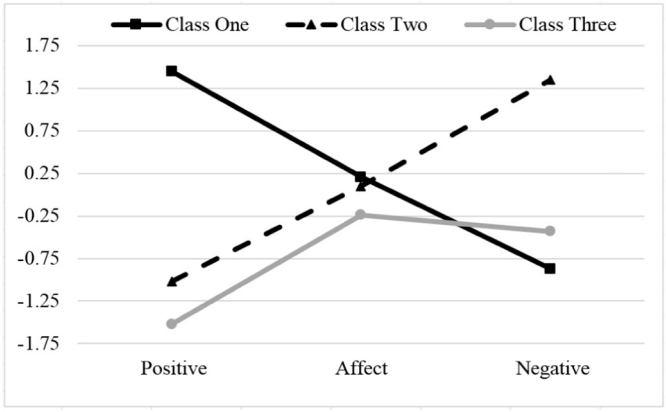


Fig. 1. Median factor scores by class membership. *Note*. Median factor score coefficients for each dimension are zero for the total sample. Statistical comparison between latent classes is available in Supplementary Table 4.

associated with positive – but not negative – symptomology. Prospective longitudinal research is needed to explore a causal relationship between intoxication effects of depressant drugs and negative symptoms in methamphetamine users.

4.1. Clinical implications

Overlooking the role of polysubstance use in the manifestation of negative symptoms may lead people with methamphetamine-associated psychotic symptoms to be misdiagnosed as having schizophrenia. A common clinical scenario may involve a patient who reports positive symptoms (i.e. delusions of persecution) precipitated by heavy methamphetamine use, as well as diminished emotional expression due to intermittent opioid use. Although these symptoms are substance-induced, such a patient would meet the symptom criteria for schizophrenia in presenting with both delusions and negative symptoms during a one-month period. Clinicians are often inclined to attribute psychotic symptoms to primary psychotic disorders rather than to substance use [43], and such misdiagnosis may result in the inappropriate prescription of long-term antipsychotic medications [44] rather than focusing on the management of substance use disorders. The findings of the current study support the need for clinicians to carefully assess each patient's drug history across all classes of substances, including licit prescription medications (such as benzodiazepines) to inform decisions about differential diagnoses. This would involve considering the number of drug types used, the timing and quantity of most recent use for each drug type, and recent changes in drug use patterns [45].

4.2. Limitations

First, the CIDI Schizophrenia module [16,46] did not include a measure of negative or disorganised psychotic symptoms [9], and therefore, some participants with a diagnosis of schizophrenia may not have been properly excluded have been captured in the negative-symptom class. Similarly, we did not screen for participants who met criteria for other primary psychotic disorders, such as bipolar disorder or schizoaffective disorder, who would report delusions or hallucinations that were not better explained by methamphetamine use (i.e. persisted for one month beyond intoxication). In the current study, these methamphetamine users would have been incorrectly identified as meeting the diagnostic criteria for SZ and confounded the symptoms profiles observed. Second, in recruiting from the community rather than clinical settings, the extracted factors may not generalise to methamphetamine users who require hospitalisation for more acute or complex psychotic symptomatology. Third, factor analysis typically requires a sample of at least 200 participants, and although this risk is reduced due to the high number of observed items and sufficient inter-item communality [47]. Finally, the current study could be strengthened with the use of a standardised tool to quantify drug use frequency in the past month, such as the Timeline Followback method [48].

4.3. Conclusions

We identified a negative symptom factor in people who use methamphetamine and who do not meet diagnostic criteria for schizophrenia. This negative syndrome was not correlated with methamphetamine use, and instead may be an artefact of depressant or sedative use. Overlooking the role of polysubstance use in people who use methamphetamine may have obfuscated diagnostic differences methamphetamine-associated psychosis and schizophrenia in prior research. Clinicians should carefully assess each patient's drug history to allow for greater accuracy when differentiating between methamphetamine-associated psychosis and schizophrenia in community settings.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2019.06.002.

References

[1] Bell D. The experimental reproduction of amphetamine psychosis. Arch Gen Psychiatry 1973;29:35–40.
[2] Srisurapanont M, Arunpongpaisal S, Wada K, Marsden J, Ali R, Kongsakon R. Comparisons of methamphetamine psychotic and schizophrenic symptoms: a differential item functioning analysis. Prog Neuro-Psychopharmacol Biol Psychiatry 2001;35(4):959–64.
[3] Angrist B, Gershon S. The phenomenology of experimentally induced amphetamine psychosis-preliminary observations. Biol Psychiatry 1970;2:95–107.
[4] Jonsson L, Sjostrom K. A rating scale for evaluation of the clinical course and symptomatology in amphetamine psychosis. Br J Psychiatry 1970;117:661–5.
[5] Lecomte T, Mueser K, MacEwan W, Thorton A, Buchanan T, Bouchard V, et al. Predictors of persistent psychotic symptoms in persons with methamphetamine abuse receiving psychiatric treatment. J Nerv Ment Dis 2013;201(12):1085–9.
[6] McKetin R, Dawe S, Burns R, Hides L, Kavanagh D, Teesson M, et al. The profile of psychiatric symptoms exacerbated by methamphetamine use. Drug Alcohol Depend 2016;161:104–9.
[7] Voce A, McKetin R, Calabria B, Burns R, Castle D. A systematic review of the symptom profile and course of methamphetamine associated psychosis. Subst Use Misuse 2019;54(4):549–59.
[8] Srisurapanont M, Ali R, Marsden J, Sunga A, Wada K, Maristela M. Psychotic symptoms in methamphetamine psychotic in-patients. Int J Neuropsychopharmacol 2003;6(4):347–52.
[9] American Psychiatric Association. Diagnostic and statistical manual of mental disorders, five edition. Arlington, VA: American Psychiatric Association; 2013.
[10] Ali R, Marsden J, Srisurapanont M, Sunga A, Baigent M, Monteiro M. Methamphetamine psychosis in Australia, Philippines, and Thailand: recommendations for acute care and clinical inpatient management. Addict Disord Treat 2010;9:143–9.
[11] Scigliano G, Ronchetti G. Antipsychotic-induced metabolic and cardiovascular side effects in schizophrenia: a novel mechanistic hypothesis. CNS Drugs 2013;27:249–57.
[12] Sax K, Strakowski S, Keck P, Upadhyaya V, West S, McElroy S. Relationships among negative, positive, and depressive symptoms in schizophrenia and psychotic depression. Br J Psychiatry 1996;168(1):68–71.
[13] Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. Br J Psychiatry 2004;185:196–204.
[14] Castle D, Buckley P. Schizophrenia, 2nd edition. Oxford: Oxford University Press; 2015.
[15] Maia T, Frank M. An integrative perspective on the role of dopamine in schizophrenia. Biol Psychiatry 2017;81:52–66.
[16] Andrews G, Peters L. The psychometric properties of the Composite International Diagnostic Interview. Soc Psychiatry Psychiatr Epidemiol 1998;33:80–8.
[17] Lukoff D, Nuechterlein K, Ventura J. Manual for the expanded brief psychiatric rating scale. Schizophr Bull 1986;12:594–602.
[18] Landis J, Koch G. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.
[19] Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, et al. The Severity of Dependence Scale (SDS) in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 1995;90:607–14.
[20] Topp L, Mattick R. Choosing a cut-off on the Severity of Dependence Scale (SDS) for amphetamine users. Addiction 1997;92:157–67.

[21] Castle D, Jablensky A, McGrath J, Carr V, Morgan V, Waterreus A, et al. The diagnostic interview for psychoses (DIP): development, reliability and applications. Psychol Med 2006;36:69–80.
[22] Muthén M. MPLUS version 7.2. computer software Los Angeles, CA: Muthén & Muthén; 2012.
[23] Tabachnick B, Fidell L. Using multivariate statistics. Boston, MA: Allyn & Bacon; 2001.
[24] Lo Y, Mendell N, Rubin D. Testing the number of components in a normal mixture. Biometrika 2001;88:767–78.
[25] Yang C. Evaluating latent class analysis models in qualitative phenotype identification. Comput Stat Data Anal 2006;50:1090–104.
[26] StataCorp. Stata statistical software: release 14. College Station, TX: StataCorp LP; 2015.
[27] Panenka W, Procyshyn R, Lecomte T, MacEwan G, Flynn S, Honer W, et al. Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Depend 2013;129(3):167–79.
[28] Dean A, Groman S, Morales A, London E. An evaluation of the evidence that methamphetamine abuse causes cognitive decline in humans. Neuropsychopharmacology 2013;38:259–74.
[29] Tomiyama G. Chronic schizophrenia-like states in methamphetamine psychosis. Jpn J Psychiatry Neurol 1990;44:531–9.
[30] Yeh H, Lee Y, Sun H, Wan S. Six months follow-up of patients with methamphetamine psychosis. Chin Med J 2001;64:388–94.
[31] Tandon R, Nasrallah H, Keshavan M. Schizophrenia, "just the facts" 4. Clinical features and conceptualization. Schizophr Res 2009;110:1–23.
[32] Rosenman S, Korten A, Medway J, Evans M. Dimensional vs. categorical diagnosis in psychosis. Acta Psychiatr Scand 2003;107:378–84.
[33] Peralta V, De Leon J, Cuesta M. Are there more than two syndromes in schizophrenia? A critique of the positive–negative dichotomy. Br J Psychiatry 1992;161:335–43.
[34] Van Os J, Fahy T, Jones P, Harvey I, Sham P, Lewis S, et al. Psychopathological syndromes in the functional psychoses: associations with course and outcome. Psychol Med 1996;26:161–76.
[35] Khantzian E. The self-medication hypothesis of substance use disorders: a reconsideration and recent applications. Harv Rev Psychiatry 1997;4(5):231–44.
[36] Padhy S, Sarkar S, Basu D, Kulhara P. Self-medication hypothesis in substance-abusing psychotic patients: can it help some subjects? Indian J Social Psychiatry 2016;32:325–31.
[37] Darke S, Hall W. Levels and correlates of polydrug use among heroin users and regular amphetamine users. Drug Alcohol Depend 1995;39:231–5.
[38] Golan D, Tashjian A, Armstrong E, Armstrong A. Principles of pharmacology: the pathophysiologic basis of drug therapy. . 2nd ed.Baltimore: LWW Publishers; 2008.
[39] de Arcos F, Verdejo-García A, Ceverino A, Montañez-Pareja M, López-Juárez E, Sánchez-Barrera M, et al. Dysregulation of emotional response in current and abstinent heroin users: negative heightening and positive blunting. Psychopharmacology 2008;198(2):159–66.
[40] Miller M, Bershad A, de Wit H. Drug effects on responses to emotional facial expressions: recent findings. Behav Pharmacol 2015;26(6):571–9.
[41] Savvas S, Somogyi A, White J. The effect of methadone on emotional reactivity. Addiction 2012;107(2):388–92.
[42] Willi T, Honer W, Thornton A, Gicas K, Procyshyn R, Rodriguez F, et al. Factors affecting severity of positive and negative symptoms of psychosis in a polysubstance using population with psychostimulant dependence. Psychiatry Res 2016;240(30):336–42.
[43] Schanzer B, First M, Dominguez B, Hasin D, Caton C. Diagnosing psychotic disorders in the emergency department in the context of substance use. Psychiatr Serv 2006;57:1468–73.
[44] Mathias S, Lubman D, Hides L. Substance-induced psychosis: a diagnostic conundrum. J Clin Psychiatry 2008;69:358–67.
[45] McIver C, McGregor C, Baigent M, Spain D, Newcombe D, Ali R. Guidelines for the medical management of patients with methamphetamine induced psychosis. Southern Adelaide Health Service, Australian Government; 2017 (Adelaide, Australia).
[46] Cooper L, Peters L, Andrews G. Validity of the Composite International Diagnostic Interview (CIDI) psychosis module in a psychiatric setting. J Psychiatr Res 1998;32:361–8.
[47] MacCallum R, Widaman K. Sample size in factor analysis. Psychol Methods 1999;4(1):84–99.
[48] Sobell LC, Sobell MB. Timeline Followback user's guide: a calendar method for assessing alcohol and drug use. Toronto, Ontario, Canada: Addiction Research Foundation; 1996.

Study Four: Latent psychotic symptom profiles amongst people who use methamphetamine – what do they tell us about existing diagnostic categories?

This study has been published as following journal article:
McKetin, R., Voce, A., Burns, R., Ali, R., Lubman, D., Baker, A., David, C. (2018). Latent psychotic symptom profiles amongst people who use methamphetamine: what do they tell us about existing diagnostic categories? *Frontiers in Psychiatry*, 9: 578.

Foreword:

Study four addressed the fourth research question of this thesis: *Are there different profiles of lifetime delusions and hallucinations among people who use methamphetamine, and how do these profiles correspond to the diagnostic criteria for schizophrenia (SZ)*? Latent class analysis was used to examine whether there are discrete profiles (or syndromes) of lifetime delusions and hallucinations among a sample of current methamphetamine users (*n*=554). In the preceding studies, I examined the psychiatric symptom profile among subpopulations of methamphetamine users (i.e. those with primary psychosis in study two; those without SZ in study three). In study four, I built upon this research by documenting the psychiatric symptom profile across the broad population of people who use methamphetamine, including people who met DSM-IV criteria for SZ. I conducted follow-up analyses to investigate how the empirically-derived profiles of psychosis correspond to a diagnosis of SZ. These findings provide insight into whether this diagnostic category sufficiently captures the heterogeneity in psychosis among this population, or rather, whether multiple diagnostic categories of psychosis (i.e. MAP) appear necessary.

frontiers in Psychiatry

ORIGINAL RESEARCH
published: 19 November 2018
doi: 10.3389/fpsyt.2018.00578

Latent Psychotic Symptom Profiles Amongst People Who Use Methamphetamine: What Do They Tell Us About Existing Diagnostic Categories?

Rebecca McKetin[1,2,3]*, *Alexandra Voce*[3], *Richard Burns*[3], *Robert Ali*[4], *Dan I. Lubman*[5], *Amanda L. Baker*[6] *and David J. Castle*[7,8]

[1] Faculty of Health Sciences, National Drug Research Institute, Curtin University, Perth, WA, Australia, [2] National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW, Australia, [3] Research School of Population Health, Australian National University, Canberra, ACT, Australia, [4] School of Medical Sciences, University of Adelaide, Adelaide, SA, Australia, [5] Turning Point, Eastern Health and Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia, [6] School of Medicine and Public Health, Faculty of Health, University of Newcastle, Callaghan, NSW, Australia, [7] St Vincent's Hospital, Fitzroy, VIC, Australia, [8] Department of Psychiatry, University of Melbourne, Melbourne, VIC, Australia

OPEN ACCESS

Edited by:
Yanping Bao,
Peking University, China

Reviewed by:
Musa Basseer Sami,
King's College London, United Kingdom
Giuseppe Carrà,
Università Degli Studi di Milano Bicocca, Italy

***Correspondence:**
Rebecca McKetin
rebecca.mcketin@curtin.edu.au

Specialty section:
This article was submitted to Addictive Disorders, a section of the journal Frontiers in Psychiatry

Received: *15 August 2018*
Accepted: *22 October 2018*
Published: *19 November 2018*

Citation:
McKetin R, Voce A, Burns R, Ali R, Lubman DI, Baker AL and Castle DJ (2018) Latent Psychotic Symptom Profiles Amongst People Who Use Methamphetamine: What Do They Tell Us About Existing Diagnostic Categories? Front. Psychiatry 9:578. doi: 10.3389/fpsyt.2018.00578

The inability to distinguish clearly between methamphetamine-related psychosis and schizophrenia has led to the suggestion that "methamphetamine psychosis" does not represent a distinct diagnostic entity but rather that the drug has triggered a vulnerability to schizophrenia. We tested this possibility by exploring the latent class structure of psychotic symptoms amongst people who use the drug and examining how these latent symptom profiles correspond to a diagnosis of schizophrenia. Latent class analysis was carried out on the lifetime psychotic symptoms of 554 current methamphetamine users, of whom 40 met the DSM-IV criteria for schizophrenia. Lifetime diagnoses of schizophrenia and individual psychotic symptoms were assessed using the Composite International Diagnostic Interview. The chosen model found 22% of participants had a high propensity to experience a wide range of psychotic symptoms (schizophrenia-like), whereas the majority (56%) more specifically experienced persecutory delusions and hallucinations (paranoid psychosis) and had a lower probability of these symptoms than the schizophrenia-like class. A third class (22%) had a low probability of all symptoms, with the exception of 34% reporting persecutory delusions. Participants in the schizophrenia-like class were more likely to meet diagnostic criteria for schizophrenia (26 vs. 3 and 1% for each of the other classes, $p < 0.001$) but the diagnosis failed to encompass 74% of this group. These results are consistent with there being a distinction between schizophrenia and methamphetamine-related psychotic symptoms, both in terms of the propensity to experience psychotic symptoms, as well as the symptom profile; however, this distinction may not be captured well by existing diagnostic classifications.

Keywords: methamphetamine, amphetamine-related disorders, psychotic disorders, schizophrenia, diagnosis, psychosis

INTRODUCTION

Both current international classification systems for mental disorders [i.e., the International Statistical Classification of Diseases and Related Health Problems (ICD), 10th Revision (1) and the Diagnostic and Statistical Manual, 5th edition, DSM-5 (2)] differentiate between psychosis related to methamphetamine use (under the diagnosis of a substance-induced psychosis) and primary psychotic disorders, such as schizophrenia. However, the commonality between the symptom profile of methamphetamine psychosis and acute paranoid schizophrenia (3, 4) often makes it difficult to make a clear diagnosis, particularly in the early stages of psychosis when prognostic information is not yet available (5, 6). This frustration has led to concerns about the clinical utility of the diagnostic categories and the potential ramifications of misdiagnosis and failure to intervene early, particularly as substance-induced presentations are often used as a justification to exclude individuals from psychiatric care (7).

Most of the previous research that has attempted to differentiate between schizophrenia and methamphetamine-related psychosis use has done so by comparing symptom profiles cross-sectionally. For example, Medhus and colleagues compared individuals presenting with psychosis by whether or not they tested positive for methamphetamine psychosis, and found no significant differences in the severity of positive symptoms (5). Hides et al. (6) similarly failed to find differences in the severity of overall positive or negative symptoms in methamphetamine users who met DSM-IV diagnostic criteria for substance-induced psychosis and those who met DSM-IV criteria for a primary psychotic disorder. Srisurapanont et al. (8) examined more specific symptoms in methamphetamine psychosis, and, using cluster analytic techniques, found evidence of negative, positive and affective symptom clusters, which were almost the same as that seen in a comparison group of patients diagnosed with schizophrenia.

This lack of a clear diagnostic boundary between methamphetamine-related psychosis and schizophrenia has led Bramness and colleagues to propose that methamphetamine psychosis does not represent a unique diagnostic entity, but would be better conceptualized as a triggering of a schizophrenia spectrum disorder in vulnerable individuals (9). This theory is couched in the stress-vulnerability framework, whereby vulnerability to psychosis occurs along a continuum of risk, and exposure to methamphetamine interacts with this latent risk to precipitate psychosis. Conceptualized within this framework, a psychosis precipitated by methamphetamine need not be considered a separate diagnostic entity from a primary psychotic disorder. This possibility opens the door for such individuals to be provided with an early intervention approach for psychosis, including antipsychotic treatment, as would be the case for individuals with a primary psychotic disorder.

On the other hand, methamphetamine use is associated with different prognostic outcomes amongst people presenting with psychosis (10–12). Case reports (13) and experimental inductions of methamphetamine psychosis (4) suggest that it is a transient phenomenon that does not warrant ongoing anti-psychotic treatment. There is also emerging evidence that the symptom profile associated with methamphetamine use can be distinguished from that associated with primary psychotic disorders, in that specific types of psychotic symptoms (particularly non-persecutory delusions) are risk markers for more persistent psychosis (14) and a diagnosis of a primary psychotic disorder (15, 16). Together, this evidence suggests a potential clinical benefit in identifying methamphetamine-related psychosis as distinct from non-organic psychotic processes.

One way to test whether there is any merit in retaining the diagnostic category of methamphetamine-induced psychosis (cf. the triggering of schizophrenia) is using latent class analysis. Latent class analysis classifies population heterogeneity into categorical groups of homogeneous individuals which may have implications for classification (i.e., diagnosis), prognosis (i.e., longitudinal course), and treatment (i.e., propensity to respond to different treatments) (17). Latent class analysis has been increasingly applied in psychiatry to identify subgroups of patients or clinical markers that may have clinical utility but which are obscured by more traditional methods of analysis, such as pairwise group comparisons that presuppose diagnostic structures and their relationship to clinical characteristics (18–20). In latent class analysis, the presence of a group of people who are homogenous in their symptom profile should present as a single latent class. The presence of more than one latent class would suggest multiple groups of individuals who are distinguishable based on their symptom profile, and would be consistent with a need for different diagnostic categories to reflect these different symptom typologies.

Here we use latent class analysis to examine whether there is evidence of different classes of psychosis amongst people who use methamphetamine, as well as to understand how these classes correspond to the diagnostic category of schizophrenia. We hypothesized that if psychosis amongst people who use methamphetamine reflects the triggering of schizophrenia, then we would detect a single latent profile of psychotic symptoms, thus reflecting the symptom profile associated with schizophrenia. Conversely, if methamphetamine induced a psychosis that was distinct from schizophrenia then this should manifest as a separate class reflecting the symptom profile associated with methamphetamine-induced psychosis. Essentially, the presence of two or more latent classes would suggest different psychosis typologies in the population, and this would be more consistent with a need for multiple diagnostic categories to capture the heterogeneity in psychosis amongst people who use methamphetamine.

MATERIALS AND METHOD

Participants and Procedure

Participants were drawn from two Australian-based studies of methamphetamine users (21, 22). Data on 178 participants were taken from a cross-sectional survey conducted in Canberra in 2016–17 of volunteers recruited from the general community (via advertisements at needle and syringe programs, online and other public locations, and word of mouth) who used methamphetamine at least monthly and who were aged 18

years or older (21). Data for a further 376 participants were drawn from a longitudinal cohort study, the Methamphetamine Treatment Evaluation Study (MATES) (22, 23), conducted in Sydney and Brisbane from 2006 to 2011, and which included 400 participants seeking treatment for methamphetamine use; and, a further 101 dependent methamphetamine users recruited from the community. MATES participants had to be 16 years or older and not have been incarcerated, in drug treatment or any in-patient treatment for the month prior to enrollment. Participants from the MATES cohort were not included if they did not meet DSM-IV criteria for methamphetamine dependence in the year prior to recruitment ($n = 17$) or they did not complete the 3-month follow-up interview where a diagnosis of schizophrenia was made ($n = 92$). Interviews were conducted face-to-face or by phone. All participants were volunteers who provided either written or verbal informed consent and were reimbursed (up to AUD40 per interview). Verbal informed consent procedures were approved by the institutional Human Research Ethics Committee.

Measures

Psychosis Measures

A DSM-IV lifetime diagnosis of schizophrenia was made using the Composite International Diagnostic Interview (CIDI) Version 2.1 (24). Negative symptoms, disorganization and catatonia were not assessed because of the difficulty assessing these symptoms retrospectively across the participant's lifespan based on current self-report. Lifetime psychotic symptoms were based on the symptom criteria for schizophrenia as assessed in the pertinent section of the CIDI (24). Delusions were grouped as persecutory, thought projection, thought interference, passivity, reference, other delusions (erotomania, jealousy, mind reading). Hallucinations were categorized as complex auditory hallucinations, other auditory hallucinations, visual hallucinations, and other hallucinations (olfactory, gustatory and tactile). See the **Supplementary material** for further detail.

Substance Use

Days of methamphetamine use and other substance use (cannabis, heroin, cocaine, ecstasy, hallucinogens, alcohol, and tobacco) in the previous 4 weeks was assessed using the Opiate Treatment Index (25). Self-reported abstinence from methamphetamine was confirmed in a sub-sample of the MATES cohort using hair toxicology, with false reporting of abstinence occurring in only 6% of cases (22). Other methamphetamine use measures included age of first use, main route of methamphetamine administration in the previous month, as well as severity of methamphetamine dependence in the previous month, assessed using the Severity of Dependence Scale (SDS) (26). Dependence on methamphetamine was defined as a score of 4 or greater on the SDS scale, which corresponds to a CIDI diagnosis of severe dependence with 71% sensitivity and 77% specificity (27). Baseline data are reported for the MATES participants.

Statistical Analysis

Latent class analysis in MPlus version 7.2 (28) was applied to the binary symptom variables using a maximum likelihood estimator with robust standard errors. Latent models were fitted using 600 random starting values to ensure replication of the final log-likelihood value. Modeling was performed sequentially by examining whether each additional class significantly improved the fit of the model to the data, as indicated by the Voung-Lo-Mendell-Rubin Likelihood Ratio Test (VLMR LRT) and the parametric bootstrapped Likelihood Ratio Test (BLRT) (29, 30). Owing to a sample size that may be sensitive to small chi-square changes, entropy, the Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) were also used to compare model fit. Consideration of all goodness of fit indices and parsimony determined the number of classes to be extracted. Participants' most likely class was determined from the latent class posterior distribution.

Other data analyses were performed using Stata SE version 14.1 (31). Group comparisons were made using a Pearson's Chi Square test for categorical data, *t*-tests for continuous data, and a median comparison test for skewed continuous data (where medians and interquartile ranges [IQR] are reported rather than means and standard deviations [SDs]). Receiver Operating Characteristics was conducted using the "roctab" command and the "pvenn2" was used to produce the related Venn diagram. All tests were two-sided with significance set at $p < 0.05$.

RESULTS

Characteristics of the Sample

Participants ($n = 554$) had a mean (SD) age of 34.3 (9.5) years, 70% were male, and 89% were Australian born. They had used methamphetamine for a mean (SD) of 15.4 (9.0) years and they had used on a median (IQR) of 14 (6–20) days in the previous month. For participants who had used methamphetamine in the previous month (95%), 86% usually took crystalline methamphetamine. The main route of administration was injection (75%), with 18% smoking and 6% swallowing or snorting the drug. The most commonly used other drugs in the previous month were tobacco (95%), cannabis (79%), and alcohol (68%), with other drugs being used less commonly (heroin 31%, ecstasy 21%, cocaine 21%, inhalants 6%, and hallucinogens 6%).

Lifetime psychotic symptoms were reported by 87% of participants, most commonly persecutory delusions (74%), auditory hallucinations (49%: 27% complex and 23% other), visual hallucinations (43%) and other hallucinations (56%) (**Table 1**). Seven percent of participants ($n = 40$) met the DSM-IV criteria for a lifetime diagnosis of schizophrenia.

Latent Class Analysis

A two-class model significantly improved fit over a one class model (**Table 2**). A three-class model further improved model fit. The three-class model was selected based on significant VLMR and LRT tests, and lower AIC and adjusted BIC (**Table 2**). A sensitivity analysis was conducted that included a covariate in the analysis that identified the study from which participants were recruited to confirm that this was not unduly influencing

TABLE 1 | Participant characteristics by latent class.

	"Schizophrenia-like" ($n = 123$)	"Paranoid psychosis" ($n = 309$)	"Few symptoms" ($n = 122$)	Total sample ($n = 554$)
SYMPTOMS (%)				
Persecutory delusions	98	80***	34***†††	74
Delusions of reference	54	10***	0***†††	18
Thought projection	74	12***	1***†††	23
Thought interference	63	4***	0***†††	16
Delusions of passivity	58	5***	1***†††	16
Other delusions	75	27***	2***†††	32
Visual hallucinations	70	49***	0***†††	43
Complex auditory hallucinations	74	17***	3***†††	27
Other auditory hallucinations	11	36***	0***†††	23
Other hallucinations[a]	85	67***	0***†††	56
DEMOGRAPHICS				
Age (median years)	33	33	35	34
Male (%)	71	69	75	71
Years of schooling (median)	10	10	10	10
Unemployed (%)	82	75	73	76
Immigrant (%)	17	8**	12	11
METHAMPHETAMINE USE				
Duration of use (median years)	15	14	15	14
Days of use (median)	14	15	13	14
Injecting (%)	80	71	71	73
SDS score (%)	9	8	7	8
Dependent (%)	81	79	74	78
OTHER DRUGS USED IN THE PAST MONTH (%)				
Tobacco	98	93*	96	95
Cannabis	82	79	78	79
Alcohol	72	69	61	68
Ecstasy	15	25*	14†	21
Cocaine	20	23	20	21
Hallucinogens	6	7	6	6
Inhalants	6	7	2	6
Heroin	28	33	30	31
No. other drug classes used in past month (mean)	3.3	3.4	3.1†	3
DSM-IV criteria for schizophrenia (%)	26	3***	0***	7

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$, relative to the schizophrenia-like class.
†$p < 0.05$, †††$p < 0.001$, relative to the paranoid psychosis class.
[a]Tactile, gustatory or olfactory.

the classes detected. A comparable pattern of results was found. Analysis of a four-class model is not reported as the highest log-likelihood value was not replicated and thus was excluded from further consideration.

The symptom profile associated with each class in the three-class model is shown in **Figure 1**, and the characteristics of each class are shown in **Table 1**. The first class (22% of participants) had a very high probability of reporting almost all types of psychotic symptoms and were significantly more likely to meet the DSM-IV criteria for schizophrenia than the other two latent classes (26 vs. 3 and 0%, respectively; **Table 1**). We labeled this group "schizophrenia-like." The majority of participants (56%) had a symptom profile that was characterized more specifically by persecutory delusions (80%) and various hallucinations (17–67%; labeled "paranoid psychosis"). Participants in this class and had a significantly lower probability of all symptom types than the schizophrenia-like group and only 3% met the DSM-IV diagnostic criteria for schizophrenia. The third class comprised a minority of participants (22%) who had a very low probability of all symptoms with the exception of 34% reporting persecutory delusions (labeled "few symptoms"); none of the participants in this class met the DSM-IV diagnostic criteria for schizophrenia.

There were few differences in the demographic or polysubstance use characteristics of the three classes. The

TABLE 2 | Model fit statistics for latent class analysis.

	Full sample ($N = 554$)	
	Two-class	**Three-class**
Class membership	1. $n = 169$ (31%) 2. $n = 385$ (69%)	1. $n = 123$ (22%) 2. $n = 309$ (56%) 3. $n = 122$ (22%)
Bootstrap LRT (*p*-value)	−7475 (<0.001)	−7119 (<0.001)
Entropy	0.796	0.761
AIC/Adjusted BIC	5498/5522	5384/5421
VLMR LRT (*p*-value)	−7475 (<0.001)	−7119 (0.003)

Akaike's information criterion (AIC), Bayesian information criterion (BIC), Voung-Lo-Mendell-Rubin (VLMR), likelihood ratio test (LRT).

paranoid psychosis class was less likely to be immigrant, more likely to use ecstasy and less likely to smoke tobacco, while the few symptom class had lower levels of polysubstance use (**Table 1**).

Receiver Operating Characteristics (ROC) Analysis

To assess concordance between the DSM-IV diagnosis of schizophrenia and the schizophrenia-like class we detected in our LCA analysis, we conducted a ROC analysis with the schizophrenia-like class ($n = 123$) as the reference variable and the DSM-IV diagnosis of schizophrenia ($n = 40$) as the class variable. Although there was significant concordance between meeting the DSM-IV criteria for schizophrenia and membership in the schizophrenia-like class (ROC area = 0.62, 95% CI 0.58–0.66), and the DSM-IV criteria had good specificity in detecting participants in the schizophrenia-like class (98%), sensitivity was poor (26%). Thus, 74% of participants who fell into the schizophrenia-like class did not meet the DSM-IV diagnostic criteria for schizophrenia (**Figure 2**).

DISCUSSION

These findings suggest the presence of three latent classes of psychosis vulnerability amongst people who use methamphetamine, including two distinct classes of individuals who have vulnerability to psychotic symptoms, but differ in both their symptom profile and their probability of psychotic symptoms. The identification of multiple relatively distinct latent classes of psychosis (i.e., different typologies of psychosis) in this population is inconsistent with the notion of a single diagnostic category, as would be expected if methamphetamine was triggering schizophrenia. Importantly, we found latent symptom profiles that aligned conceptually with the existing diagnostic groupings of schizophrenia and methamphetamine-induced psychosis. Specifically, the larger of the two groups had a symptom profile comprised of persecutory delusions and hallucinations, consistent with the classic notions of methamphetamine-induced psychosis (32). In contrast, a minority of people who used the drug had a comparatively high probability of all psychotic symptoms and were significantly more likely to meet the DSM-IV diagnostic criteria for schizophrenia.

The presence of multiple latent psychotic symptom profiles in this population does not preclude a common etiology for psychosis vulnerability, in the sense that different psychotic symptom profiles could plausibly stem from a common underlying vulnerability, as suggested by Bramness et al. (9). For example, influenza results in symptom clusters in multiple organ systems, which present at different time in the course of the illness, and can vary in how they are expressed between individuals. However, the reliance on clinical syndromes over etiological mechanisms to define psychiatric disorders means that diagnostic categories need to carry weight in their usefulness to describe and treat patients, and to understand their likely prognosis. In this sense, our data suggest that there are meaningfully different sub-populations of psychosis amongst people who use methamphetamine (both in terms of their propensity to experience psychotic symptoms and their symptom profile). Further research is needed to determine the prognostic utility of these identified typologies and how they could be better captured using diagnostic criteria.

Although the identified classes of psychosis vulnerability bear some resemblance to existing diagnostic categories, individuals who had a high probability of psychosis (the schizophrenia-like class) were not sufficiently well captured by the diagnostic criteria for schizophrenia, or at least not as they are assessed through the CIDI. This lack of sensitivity to identify methamphetamine users who have a high probability of psychosis is likely to underpin the challenges faced by clinicians in being able to apply diagnostic criteria to identify individuals who would benefit from early intervention strategies for a psychotic disorder (7). That said, we also show that the majority of individuals who use methamphetamine do not reach a threshold of symptom severity associated with schizophrenia, and this has potentially important implications for treatment, in that these individuals may not benefit from sustained antipsychotic treatment and may require a different model of care.

The poor sensitivity of the diagnostic criteria for schizophrenia to detect individuals who we identified as having a schizophrenia-like psychosis is likely to be due to the poor sensitivity of the CIDI to detect schizophrenia (relative to clinician ratings) more generally (33). However, it could also reflect poor sensitivity of the DSM criteria in the context of comorbid methamphetamine use. The latter view has been flagged by researchers and clinicians (7), and suggested by prospective data, in which 30% of individuals initially diagnosed with an amphetamine-related psychosis are re-diagnosed with a primary psychotic disorder within 10 years (34). The existence of this orphan category of individuals who had a high probability of psychosis, but who failed to meet the DSM-IV criteria for schizophrenia, may explain clinical descriptions of a persistent or prolonged form of psychosis amongst people who use methamphetamine (as distinct from schizophrenia), and that this phenomena shares commonality with schizophrenia both in terms of its familial morbidity (35) and symptom profile (14). These individuals may have an underlying vulnerability to schizophrenia that is triggered by methamphetamine, or

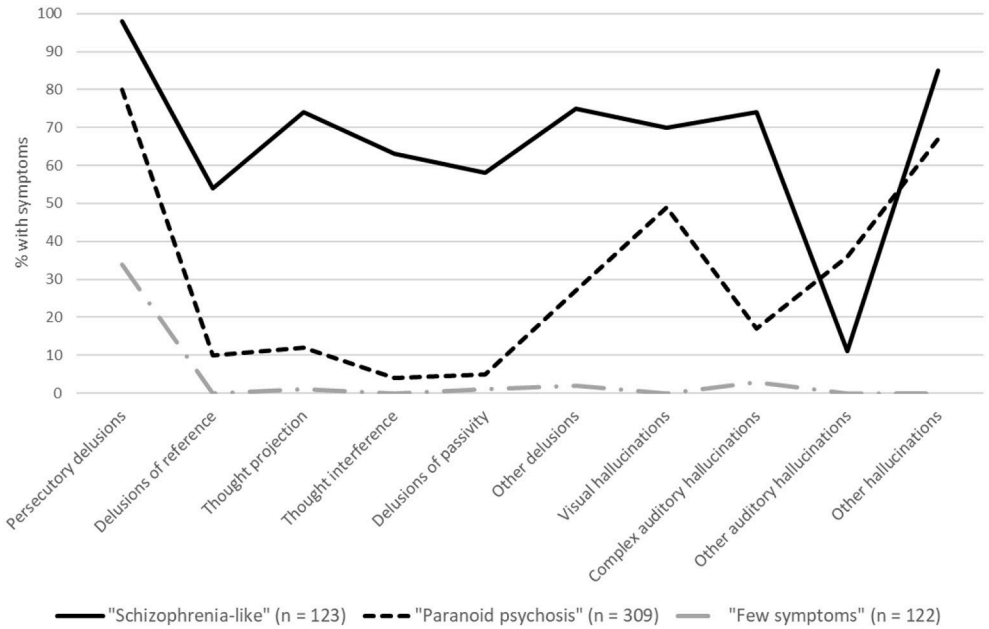


FIGURE 1 | Lifetime symptom prevalence for the three-class model.

conversely, are using the drug as a form of self-medication to manage a premorbid vulnerability or prodromal state.

Our finding suggest that assessing the past experience of specific types of psychotic symptoms may help to identify methamphetamine-related psychosis patients who would benefit from an early intervention for a psychotic disorder. Specifically, we found a broader symptom profile (i.e., presence of non-persecutory delusions and complex auditory hallucinations) amongst individuals who had a schizophrenia-like psychosis profile. This finding aligns with our previous research which found that the presence of these symptoms was associated with psychosis that persisted beyond methamphetamine use and that their presence in first episode psychosis portended a subsequent diagnosis of schizophrenia (14–16). Conversely, evidence of a second class of people with paranoid psychosis, similar to the current conceptualization of methamphetamine-induced psychosis, suggests that individuals who report having only ever experienced persecutory delusions (with or without hallucinations) are likely to be at much lower risk of having schizophrenia and may benefit more from substance use treatment to reduce their risk of subsequent psychotic episodes rather than ongoing antipsychotic treatment. A caution here is that we did not have prognostic data available to validate the clinical utility of the latent classes of psychosis that we detected. For this reason we suggest that the monitoring of symptoms, including their response to clinical interventions, remains imperative.

The presence of a sub-group of individuals who report having experienced few psychotic symptoms, or only paranoia, suggests differential vulnerability to methamphetamine-related psychosis. This observation is consistent with previous literature showing that not all people who use the drug develop psychotic

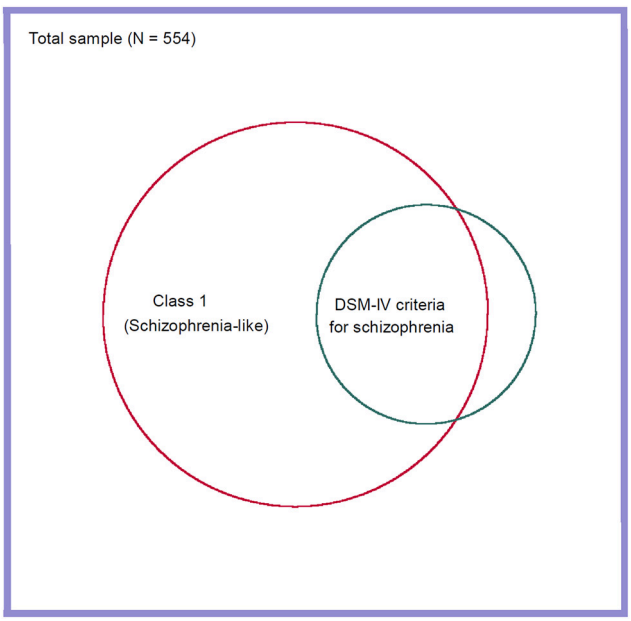


FIGURE 2 | Venn diagram showing overlap between the schizophrenia-like class and a DSM-IV diagnosis of schizophrenia.

symptoms (36) and the continuum of psychosis vulnerability observed at a population level, this owing to the many genetic and environmental factors thought to contribute to psychosis risk (37). The preponderance of persecutory delusions across all classes of psychosis vulnerability, even amongst participant with no other psychotic symptoms, may reflect suspiciousness related to the illicit-drug using context (e.g., fear of retribution, social

conflict, police surveillance). It could also reflect a continuum of vulnerability whereby persecutory delusions are expressed at lower levels of psychosis proneness, and conversely, that higher levels of vulnerability are required for the expression of hallucinations and non-persecutory delusions (36).

A limitation of the current study was that schizophrenia was the only primary psychotic disorder diagnosed and only a small number of participants met the criteria for this disorder. However, we did not exclude psychotic symptoms that occurred in the context of depression or mania when making this diagnosis, and therefore any participants meeting the symptom criteria for positive symptoms (i.e., presence of delusions and/or hallucinations) in the context of these affective disturbances would have been captured under a diagnosis of schizophrenia. In addition, we used a DSM-IV diagnosis of schizophrenia (cf. DSM-5) and we did not include negative symptoms, or symptoms of disorganization or catatonia when making the diagnosis. The inclusion of these symptoms may have improved alignment between the diagnosis of schizophrenia and our high probability of psychosis sub-population, as some of these symptoms have been shown to differentiate between sub-classes of psychosis proneness and predict conversion to psychotic disorders (20). Finally, we did not attempt to diagnose substance-induced psychosis in this sample, so although we observed a symptom profile consistent with methamphetamine-related psychosis, we cannot confirm whether these participants would have met criteria for this disorder.

The finding that immigrants had a higher probability of psychosis is consistent with migration being a risk factor for psychosis (38), but it may also reflect racial differences in psychosis risk. It is important to note that our sample consisted of mostly Australian born individuals, and this may affect how the findings generalize to other racial groups and cultures. There was also a high rate of polysubstance use, including cannabis use, in this sample. Cannabis use in particular has been related to increased risk of developing a psychotic disorder (39, 40), and more cannabis frequent use is associated with an elevated occurrence of psychotic symptoms amongst people who use methamphetamine (23). However, we did not find any evidence of greater polysubstance use, including cannabis use, amongst participants who had a high probability of psychosis in this sample.

In sum, we demonstrate the importance of retaining the diagnostic category of methamphetamine-related psychosis (i.e., substance-induced psychosis in the DSM-5) as an alternative to schizophrenia, as it is clear that the majority of people who use methamphetamine have a relatively low propensity to experience psychotic symptoms that would meet the criteria for schizophrenia, and have a different symptom typology. Prognostic data would be needed to confirm the full diagnostic utility of these latent sub-populations of psychosis vulnerability. However, the cross-sectional perspective provided here cautions against assuming that all psychosis arising in the context of methamphetamine use reflects schizophrenia. In addition, we found that the DSM-IV diagnostic criteria for schizophrenia had limited utility for identifying methamphetamine users who had a high probability of psychosis, suggesting that further development of the criteria are needed to improve the detection of psychotic disorders in this population.

ETHICS STATEMENT

The research was approved by the Australian National Human Research Ethics Committee (2015/638). All participants provided verbal informed consent prior to participation. Verbal consent rather than written consent was obtained in order to protect the confidentiality of participants.

AUTHOR CONTRIBUTIONS

RM was the lead investigator on the two studies from which the data were drawn; she conceived of and drafted the manuscript. AV collected survey data and conducted the latent class analysis. RB, DC, and RM provided Ph.D. supervision to AV in undertaking these activities. AB, DL, and RA were investigators on the MATES cohort. All authors have contributed to the drafting of the final manuscript.

FUNDING

MATES was funded by the Australian National Health and Medical Research Council (Project Grant No. 350974) and the Australian Government Department of Health and Aging, was conducted by the National Drug and Alcohol Research Centre at the University of New South Wales, with contributions from other project investigators (Joanne Ross, Jake Najman, RA, Sharon Dawe, and Nicole Lee), research staff (Shelley Cogger, Erin Kelly, Kate Hetherington, Grace Ho, Cathie Sammut, Sagari Sarkar, Rachel Sutherland, Miriam Wyzenbeek, and Julia Rosenfeld), participating treatment agencies and participants. Other data collection was funded by ACT Health.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2018.00578/full#supplementary-material

REFERENCES

1. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva: World Health Organization (1992).
2. Association AP. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed Arlington, VA: American Psychiatric Publishing (2013).
3. Angrist BM, Gershon S. The phenomenology of experimentally induced amphetamine psychosis–preliminary observations. *Biol Psychiatry* (1970) 2:95–107.
4. Bell DS. The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry* (1973) 29:35–40. doi: 10.1001/archpsyc.1973.04200010020003
5. Medhus S, Mordal J, Holm B, Morland J, Bramness JG. A comparison of symptoms and drug use between patients with methamphetamine associated

psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. *Psychiatry Res*. (2013) 206:17–21. doi: 10.1016/j.psychres.2012.09.023
6. Hides L, Dawe S, Mcketin R, Kavanagh DJ, Young RM, Teesson M. et al. Primary and substance-induced psychotic disorders in methamphetamine users. *Psychiatry Res*. (2015) 226:91–6. doi: 10.1016/j.psychres.2014.11.077
7. Mathias S, Lubman DI, Hides L. Substance-induced psychosis: a diagnostic conundrum. *J Clin Psychiatry* (2008) 69:358–67. doi: 10.4088/JCP.v69n0304
8. Srisurapanont M, Arunpongpaisal S, Wada K, Marsden J, Ali R, Kongsakon R. Comparisons of methamphetamine psychotic and schizophrenic symptoms: a differential item functioning analysis. *Prog Neuropsychopharmacol Biol Psychiatry* (2011) 35:959–64. doi: 10.1016/j.pnpbp.2011.01.014
9. Bramness JG, Gundersen OH, Guterstam J, Rognli EB, Konstenius M, Loberg EM, et al. Amphetamine-induced psychosis–a separate diagnostic entity or primary psychosis triggered in the vulnerable?. *BMC Psychiatry* (2012) 12:221. doi: 10.1186/1471-244X-12-221
10. Curran C, Byrappa N, Mcbride A. Stimulant psychosis: systematic review. *Br J Psychiatry* (2004) 185:196–204. doi: 10.1192/bjp.185.3.196
11. Carra G, Johnson S, Crocamo C, Angermeyer MC, Brugha T, Azorin JM, et al. Psychosocial functioning, quality of life and clinical correlates of comorbid alcohol and drug dependence syndromes in people with schizophrenia across Europe. *Psychiatry Res*. (2016) 239:301–7. doi: 10.1016/j.psychres.2016.03.038
12. Sara GE, Burgess PM, Malhi GS, Whiteford HA, Hall WC. The impact of cannabis and stimulant disorders on diagnostic stability in psychosis. *J Clin Psychiatry* (2014) 75:349–56. doi: 10.4088/JCP.13m08878
13. Connell PH. Clinical manifestations and treatment of amphetamine type of dependence. *J Am Med Assoc*. (1966) 196:718–23.
14. Mcketin R, Gardner J, Baker AL, Dawe S, Ali R, Voce A. et al. Correlates of transient versus persistent psychotic symptoms among dependent methamphetamine users. *Psychiatry Res*. (2016) 238:166–71. doi: 10.1016/j.psychres.2016.02.038
15. Mcketin R, Baker AL, Dawe S, Voce A, Lubman DI. Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Res*. (2017) 251:349–54. doi: 10.1016/j.psychres.2017.02.028
16. McKetin R, Hides L, Kavanagh DJ, Saunders JB, Dawe S. First psychotic episode risk markers for primary psychosis amongst people who use methamphetamine. *Schizophr Res*. (2018) 199:456–7. doi: 10.1016/j.schres.2018.04.021
17. Lanza ST, Rhoades BL. Latent class analysis: an alternative perspective on subgroup analysis in prevention and treatment. *Prev Sci*. (2013) 14:157–68. doi: 10.1007/s11121-011-0201-1
18. Murray V, Mckee I, Miller PM, Young D, Muir WJ, Pelosi AJ. et al. Dimensions and classes of psychosis in a population cohort: a four-class, four-dimension model of schizophrenia and affective psychoses. *Psychol Med*. (2005) 35:499–510. doi: 10.1017/S0033291704003745
19. Pignon B, Peyre H, Szoke A, Geoffroy PA, Rolland B, Jardri R, et al. A latent class analysis of psychotic symptoms in the general population. *Aust N Z J Psychiatry* (2018) 52:573–84. doi: 10.1177/0004867417744255
20. Ryan AT, Addington J, Bearden CE, Cadenhead KS, Cornblatt BA, Mathalon DH, et al. Latent class cluster analysis of symptom ratings identifies distinct subgroups within the clinical high risk for psychosis syndrome. *Schizophrenia Res*. (2018) 197:522–30. doi: 10.1016/j.schres.2017.12.001
21. McKetin R, Voce A, Burns R. *Research into Methamphetamine Use in the Australian Capital Territory Perth*. Perth: National Drug Research Institute, Curtin University (2017). p. 1–58.
22. McKetin R, Najman J, Baker A, Lubman D, Dawe S, Ali R, et al. Evaluating the impact of community-based treatment options on methamphetamine use: findings from the Methamphetamine Treatment Evaluation Study (MATES). *Addiction* (2012) 107:1998–008. doi: 10.1111/j.1360-0443.2012.03933.x
23. McKetin R, Lubman DI, Baker AL, Dawe S, Ali RL. Dose-related psychotic symptoms in chronic methamphetamine users: evidence from a prospective longitudinal study. *JAMA Psychiatry* (2013) 70:319–24. doi: 10.1001/jamapsychiatry.2013.283
24. Andrews G, Peters L. The psychometric properties of the composite international diagnostic interview. *Soc Psychiatry Psychiatr Epidemiol*. (1998) 33:80–8. doi: 10.1007/s001270050026
25. Darke S, Hall W, Wodak A, Heather N, Ward J. Development and validation of a multi-dimensional instrument for assessing outcome of treatment among opiate users: the opiate treatment index. *Br J Addict*. (1992) 87:733–42. doi: 10.1111/j.1360-0443.1992.tb02719.x
26. Gossop M, Darke S, Griffiths P, Hando J, Powis B, Hall W, et al. The Severity of dependence scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. *Addiction* (1995) 90:607–14. doi: 10.1046/j.1360-0443.1995.9056072.x
27. Topp L, Mattick RP. Choosing a cut-off on the severity of dependence scale (SDS) for amphetamine users. *Addiction* (1997) 92:839–45. doi: 10.1111/j.1360-0443.1997.tb02953.x
28. Muthén M. *MPLUS Version 7.2 [Computer Software]*. Los Angeles, CA: Muthén & Muthén (2012).
29. Lo Y, Mendell N, Rubin D. Testing the number of components in a normal mixture. *Biometrika* (2001) 88:767–78. doi: 10.1093/biomet/88.3.767
30. Yang C. Evaluating latent class analysis models in qualitative phenotype identification. *Comput Stat Data Anal*. (2006) 50:1090–104. doi: 10.1016/j.csda.2004.11.004
31. Stata Corporation. *Stata/SE 14.1 for Windows*. College Station, TX: StataCorp LP (2016).
32. McKetin R. Methamphetamine psychosis: insights from the past. *Addiction* (2018) 113:1552–27. doi: 10.1111/add.14170
33. Cooper L, Peters L, Andrews G. Validity of the composite international diagnostic interview (CIDI) psychosis module in a psychiatric setting. *J Psychiatr Res*. (1998) 32:361–8. doi: 10.1016/S0022-3956(98)00021-1
34. Niemi-Pynttari J, Sund R, Putkonen H, Vorma H, Wahlbeck K, Pirkola S. Substance-induced psychosis converting into schizophrenia: a register-base study of 18,478 Finnish inpatient cases. *J Clin Psychiatry* (2013) 74:e94. doi: 10.4088/JCP.12m07822
35. Chen CK, Lin SK, Sham PC, Ball D, Loh El W, Murray RM. Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *Am J Med Genet B Neuropsychiatr Genet*. (2005) 136B:87–91. doi: 10.1002/ajmg.b.30187
36. Arunogiri S, Foulds JA, Mcketin R, Lubman DI. A systematic review of risk factors for methamphetamine-associated psychosis. *Aust N Z J Psychiatry* (2018) 52:514–29. doi: 10.1177/0004867417748750
37. Van Os J, Linscott RJ, Myin-Germeys I, Delespaul P, Krabbendam L. A systematic review and meta-analysis of the psychosis continuum: evidence for a psychosis proneness-persistence-impairment model of psychotic disorder. *Psychol Med*. (2009):39:179–95. doi: 10.1017/S0033291708003814
38. Mcgrath J, Saha S, Welham J, El Saadi O, Maccauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med*. (2004) 2:13. doi: 10.1186/1741-7015-2-13
39. Castle DJ. Cannabis and psychosis: what causes what?. *F1000 Med Rep*. (2013) 5:1. doi: 10.3410/M5-1
40. Hall W, Degenhardt L. Cannabis use and the risk of developing a psychotic disorder. *World Psychiatry* (2008) 7:68–71. doi: 10.1002/j.2051-5545.2008.tb00158.x

Conflict of Interest Statement: DL has provided consultancy advice to Lundbeck and Indivior, and has received travel support and speaker honoraria from Astra Zeneca, Indivior, Janssen, Lundbeck, Servier, and Shire.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Study Five: A latent class analysis of psychiatric symptom profiles associated with past-month methamphetamine use

This study is based on the publication:
Voce, A., Burns, R., Castle D., Calabria, B., & McKetin, R. (2021). A latent class analysis of psychiatric symptom profiles associated with past-month methamphetamine use. *Psychiatry Research, 298,* 113760.

Foreword:

Study five addressed the final research question of this thesis: *Are there different profiles of psychiatric symptoms among people who use methamphetamine, and how do these profiles represent people with SZ and people with MAP*? Using latent class analysis, I investigated whether there are separate profiles (or syndromes) of psychiatric symptoms among 160 people who used methamphetamine in the past month. To build upon the previous study, I measured a much wider range of symptoms (including affective, activation/disorganised, negative, and positive psychotic symptoms) within the past-month (rather than lifetime). It is important to understand how syndromes of psychosis manifest in current symptomatology, as clinicians would typically observe an individual's current psychiatric presentation when making diagnostic judgements. To inform an understanding of whether MAP is a distinct disorder from SZ, I examined whether different latent profiles represented people who met lifetime diagnostic criteria for SZ relative to those who met lifetime diagnostic criteria for MAP.

Psychiatry Research 298 (2021) 113760

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

A latent class analysis of psychiatric symptom profiles associated with past-month methamphetamine use

Alexandra Voce [a,*], Richard Burns [a], David Castle [b,c], Bianca Calabria [d,e], Rebecca McKetin [e]

[a] Centre for Research on Ageing, Health and Wellbeing, Australian National University, Building 54, Mills Road, Acton, ACT 2601, Australia
[b] Centre for Complex Interventions, Centre for Addictions and Mental Health, Toronto, Canada
[c] University of Toronto, Toronto, Canada
[d] Research School of Population Health, Australian National University, Building 54, Mills Road, Acton, ACT 2601, Australia
[e] National Drug and Alcohol Research Centre, University of New South Wales, 22 King Street, Randwick, NSW 2031, Australia

ARTICLE INFO

Keywords:
Amphetamine
Stimulants
Schizophrenia
Methamphetamine-related
Substance-induced
Methamphetamine-associated
Drug-induced

ABSTRACT

We explored latent psychiatric symptom profiles associated with methamphetamine use, and examined how these corresponded to diagnoses of schizophrenia (SZ) and methamphetamine-associated psychosis (MAP). We assessed psychiatric symptoms among 160 people who had used methamphetamine in the past month. Psychiatric symptoms were defined as a score of 4+ on Brief Psychiatric Rating Scale (BPRS) items. Diagnoses were made using the Composite International Diagnostic Interview (CIDI). Participants were defined as having MAP if they met symptom criteria for SZ, but symptoms were considered to be always the result of substance use. Latent class analysis identified three classes. Class one (44% of participants) had a low probability of most BPRS symptoms; 4% met criteria for SZ, 51% for MAP. Class two (31% of participants) had a higher probability hallucinations and suspiciousness (37–46%); 72% met criteria for MAP, and 7% for SZ. Class three (25% of participants) had the highest probability for all positive psychotic symptoms (hallucinations, suspiciousness, grandiosity, unusual thought content; 32–82%), and reported activation, conceptual disorganisation, and tension (35% met criteria for SZ and 17% for MAP). We found three distinct classes of psychiatric symptom profiles, two of which showed partial alignment with diagnostic constructs of SZ and MAP.

1. Introduction

People who engage in heavy long-term use of methamphetamine comprise a complex clinical population, with elevated rates of comorbid primary psychotic disorders such as schizophrenia (SZ; Akindipe et al., 2014; Sara et al., 2015). Among those without a primary psychotic disorder (endogenous to the person), 43% of people dependent on methamphetamine experience a transient psychotic syndrome (Lecomte et al., 2018), referred to here as methamphetamine-associated psychosis (MAP; Glasner-Edwards et al., 2008; Grant et al., 2012). To meet the DSM-5 diagnostic criteria for MAP (American Psychiatric Association [APA]; 2013), individuals must experience delusions and hallucinations (i.e. positive psychotic symptoms) that are deemed to be aetiologically related to methamphetamine use (e.g., occur during or subsequent to methamphetamine use, not persist for a substantial period after cessation of methamphetamine use, and not be better accounted for by a pre-existing non-organic psychosis or other medical condition). A diagnosis of SZ can be appropriate when positive psychotic symptoms are present and not better explained by substance use. Unlike MAP, a diagnosis of SZ can also be based on other (non-essential) symptoms, including disorganised speech, grossly disorganised or catatonic behaviour, and negative symptoms (i.e. diminished emotional expression or avolition), and it requires continous signs of disturbance to persist for a period of six months or more (APA, 2013). Not all cases of methamphetamine-related psychosis fit neatly into these diagnostic categories. A proportion of people experience persistent symptoms of psychosis following methamphetamine use, but do not meet the full criteria for SZ (McKetin et al., 2016; Voce at al., 2019a). Distinguishing between SZ and MAP in clinical settings is notoriously difficult (Mathais et al. 2008) and 25–38% of patients initially diagnosed with MAP in clinical settings are subsequently rediagnosed with schizophrenia (Kittirattanapaiboon et al, 2010; Medhus et al, 2015; Niemmi Pyntarri et al, 2013).

Although separate aetiological mechanisms are theorised to

* Corresponding author.
E-mail address: alexandra.voce@anu.edu.au (A. Voce).

https://doi.org/10.1016/j.psychres.2021.113760
Received 20 April 2020; Accepted 23 January 2021
Available online 27 January 2021

underpin SZ and MAP (Flaum & Schultz, 1996), these conditions can be virtually identical in cross-sectional presentation (Bell, 1965; Medhus et al., 2013); both are characterised by prominent delusions of persecution and reference, auditory, and visual hallucinations. Notably, disorganised speech and behaviour are featured in the diagnostic criteria for SZ, but not MAP, and yet these symptoms are observed in both disorders. Moreover, several studies suggest that some genetic and familial risk factors are common to both disorders (Arunogiri et al., 2018; Ikeda et al., 2013), as people with MAP are more likely to report a history of SZ among their biological relatives compared with methamphetamine users with no history of psychosis (Chen et al., 2005).

The overlapping characteristics between MAP and SZ have led some to argue that these conditions are not separate clinical entities, but rather, that MAP is SZ precipitated by methamphetamine use among vulnerable people (Bramness et al., 2012). In other words, MAP and SZ may be better represented as quantitative (rather than qualitative) differences on a disease continuum. This hypothesis aligns with the argument that traditional approaches of classifying psychotic disorders into discrete categories draws artificial boundaries around psychotic phenomena that are actually continuous in nature (Cuthbert & Insel, 2010; Morris et al., 2016). Instead, it is argued that conceptualising psychotic disorders as interrelated phenomena on a continuum (or several continua) would be a more valid approach to understanding the aetiological and pathophysiological structure of psychosis (Potuzak, et al., 2012). On the other hand, this does not necessarily mean that distribution of etiological influences underlying this continuum is also continuous. Kendler and colleagues (2019) has recently found differences in the familial risk for those with substance-induced psychosis and SZ: while familial risk for SZ predicts progression from substance-induced psychosis to SZ, people with substance-induced psychosis who do not develop SZ have a comparatively lower familial risk for SZ and relative higher familial risk for substance use disorders.When investigating whether existing diagnostic categories capture the true heterogeneity in symptoms among a population, it can be informative to explore psychiatric profiles derived directly from the data. Latent class analysis (LCA) is a data-driven statistical technique that identifies classes of individuals (i.e. subpopulations) who exhibit similar profiles of item endorsement (e.g. psychiatric symptoms). Using LCA, McKetin and colleagues (2018) derived three latent classes among people who use methamphetamine based on their lifetime profiles of positive psychotic symptoms. This included a "schizophrenia-like" class (22% of people) with a high likelihood of experiencing multiple types of delusions and hallucinations, differentiated from a "paranoid psychosis" class (56% of people) who experienced persecutory delusions and hallucinations, but at a lower likelihood than the schizophrenia-like class. The schizophrenia-like class not only exhibited a different profile of symptoms compared with the paranoid psychosis class, but also captured a majority of people who met diagnostic criteria for SZ. These results are consistent with the argument that multiple diagnostic categories are needed to describe the heterogeneity in psychosis among people who habitually use methamphetamine.

To provide a diagnosis of MAP or SZ, a clinician will typically observe an individual's current psychiatric presentation, and assess prior psychiatric history (APA, 2013). Thus, to judge the clinical utility of a diagnostic category for MAP, further work is needed to test whether multiple profiles (i.e. syndromes) emerge when applying LCA to current (rather than lifetime) symptoms. Peralta and colleagues (2002) found a low level of concordance between latent class models when applied to lifetime, relative to past-month, ratings of psychotic symptoms. Those authors concluded that symptom profiles derived through LCA are highly dependent on the period of assessment, possibly because observing current symptoms allows for better differentiation between the unique profiles of people with early-stage psychoses relative to chronic long-term psychoses. When formulating psychotic disorder diagnoses, clinicians will also assess a broad range of signs and symptoms beyond delusions and hallucinations (APA, 2013). It is particularly informative to evaluate disorganised speech, disorganised behaviour, and negative symptoms, as these are listed within the diagnostic criteria for SZ. Thus, incorporating these symptoms (measured in the current episode) may improve the demarcation between latent classes, provide a more precise and complete account of profiles (or syndromes) of psychotic symptoms in this population, and reveal how these clinical groups may present differently in clinical settings.

The present study examines whether there are different profiles (or syndromes) of psychotic symptoms among people who use methamphetamine, based on their current (past-month) profiles of psychiatric symptoms. Based on the current diagnostic distinction between MAP and SZ, we expect to identify at least two classes of distinct latent psychiatric symptoms that align with each of these disorders. This finding would support the utility of having multiple diagnostic constructs for psychosis (i.e. a separate category for MAP) in this population. Alternatively, if all individuals with psychotic symptoms are represented in a single latent class, this would suggest that all psychoses associated with methamphetamine use (i.e. MAP and SZ) are better conceptualised as one common clinical entity with a shared symptom profile. We also examine how these profiles align with the DSM-IV lifetime diagnostic criteria for SZ and MAP.

2. Method

2.1. Procedure

Participants were people who used methamphetamine who were recruited through word-of-mouth, and through advertising on public flyers, in local magazines, and online. All participants were volunteers who provided oral informed consent and were reimbursed AU$40. The study was approved by the Australian National University's Human Research Ethics Committee and conducted in Canberra, Australia. For recruitment into the study, participants had to be at least 18 years of age, have used illicit methamphetamine on at least six occasions over the previous 6 months, and had not been incarcerated, hospitalised or in residential drug treatment during the month prior to interview. This final criterion was necessary to obtain a naturalistic picture of substance use in the previous month. For inclusion in the current analysis, participants had to have also used methamphetamine during the past month to ensure that measures of methamphetamine use corresponded to the past-month timeframe used to measure psychiatric symptoms. From the original sample of 189 participants, those who had not used methamphetamine in the previous month (n=11), did not complete the Brief Psychiatric Rating Scale Extended Version (BPRS-E; n=2), or did not exhibit any clinically significant symptoms on the BPRS-E (n=16) were excluded from all analyses. This gave a final sample of 160 participants.

2.2. Measures

2.2.1. Drug use

Drug use measures included the number of days of use in the previous four weeks for methamphetamine and all other major drug classes, using questions from the Opiate Treatment Index (Darke et al., 1991). Other drug measures included the main form of methamphetamine used (crystalline, powdered, or other), route of administration in the previous month (injection, smoking, snorting, or swallowing), and age at first methamphetamine use. Methamphetamine dependence in the previous month was defined as a score of four or greater on the Severity of Dependence Scale (Gossop et al., 1995). This definition yields 71% sensitivity and 77% specificity against a DSM-IV diagnosis of amphetamine dependence (Topp & Mattick, 1997).

2.2.2. Psychiatric symptoms

Psychiatric symptoms in the previous month were assessed using 24 items on the Brief Psychiatric Rating Scale Extended (BPRS-E; Ventura et al., 1993), and scored in severity from 1 ("not present") to 7

("extremely severe"). Current symptoms were defined as a score of four or greater on each item, which is the BPRS cut-off used to identify clinically significant symptoms (Lukoff et al., 1986). Four items (disorientation, uncooperativeness, mannerisms, and motor retardation) were reported by under three percent (n=5) of the sample. These items were excluded from further analyses because including items with very low endorsement can make LCA models unstable (Nylund-Gibson & Choi, 2018). A selection of interviews was audiotaped (n=21) and rated by a second interviewer (RM) for interrater reliability. Cohen's kappa values were at an acceptable level for all binary symptoms, other than elevated mood and bizarre behaviour (< 0.40) (Landis & Koch, 1977); hence, these items were excluded from the LCA. Interrater agreement for binary ratings of the remaining psychiatric symptoms was substantial (agreement = 0.85 – 0.95; kappa = 0.44 – 0.90). When describing results, these 18 symptoms were grouped in reference to four subscales identified by Dazzi and colleagues (Dazzi et al., 2016). These included anxiety, guilt, depression, and suicidality (affective symptoms); hallucinations, unusual thought content, suspiciousness, and grandiosity (positive symptoms); blunted affect and emotional withdrawal (negative symptoms); excitement, motor hyperactivity and distractibility (activation symptoms), and conceptual disorganisation, tension, hostility, self-neglect, and somatic concerns.

2.2.3. Lifetime diagnosis of SZ

A lifetime DSM-IV diagnosis of SZ was generated using the Schizophrenia Module of the Composite International Diagnostic Interview (CIDI; Andrews & Peters, 1998). DSM-IV (APA, 1994) diagnoses of SZ were based on measures of positive psychotic symptoms (SZ criteria A1–A2), functional impairment (SZ criteria B), illness duration (SZ criteria C), and medical or substance use exclusions (SZ criteria E). The diagnosis did not consider negative or disorganisedsymptoms (SZ criteria A3–A5), and diagnoses did not exclude diagnoses of bipolar disorder or schizoaffective disorder (SZ criteria D). A DSM-IV diagnosis of SZ using the CIDI corresponds to 50-95% specificity and 20-93% sensitivity against diagnostic ratings made by experienced clinicians (Cooper et al., 1998).

2.2.4. Lifetime methamphetamine-associated psychosis (MAP)

Lifetime psychosis associated with methamphetamine use (MAP) was assessed using items from the CIDI Schizophrenia module (relating to DSM-IV diagnostic criteria for SZ). Participants were defined as having MAP if they (i) had delusions or hallucinations that met symptom criteria for SZ (SZ criteria A1–A2), (ii) psychotic symptoms were always the result of substance use (SZ criteria E), (iii) psychotic symptoms were not the result of a physical illness or injury (SZ criteria E), (iv) psychotic symptoms resulted in clinically significant distress or impairment in social, occupational, or other important areas of functioning (SZ criteria B), and (v) they did not meet full DSM-IV criteria for SZ based on the CIDI module. Of those who met this criteria for MAP (n=78), 87% (n=68) reported that psychotic symptoms were due to methamphetamine or amphetamines, a further 6% (n=5) cited methamphetamine use in combination with other substances (cannabis, LSD, and alcohol), and 6% (n=5) did not report the substance involved. See Supplementary Table 1 for further detail.

2.2.5. Other measures

Using a module from the Diagnostic Interview for Psychosis (DIP; Castle et al., 2006), participants were asked whether any first- or second-degree blood relatives had a history of SZ or non-psychotic affective disorder (such as depression or anxiety). Demographic measures included age in years, sex, completed years of schooling, current employment status, formal post-secondary qualifications, incarceration history, current living arrangement, and main source of income in the previous month.

2.2.6. Statistical analyses

Latent class analysis in MPlus v7.2 (Muthén, 2012) was applied to the binary BPRS-E variables (i.e. symptom present at a severity of four or higher) to identify mutually exclusive classes of participants who presented with similar patterns of specific psychiatric symptoms. The latent classes were extracted by maximizing between-class differences and minimizing the within-class differences (Muthén, 2004). Preferred models are those with higher entropy, and lower Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) scores. The Voung-Lo-Mendell-Rubin (VLMR) likelihood ratio test and Lo-Mendell-Rubin (LMR) likelihood ratio test were used to examine whether models with additional classes significantly improved the fit of the model to the data (Lo et al., 2001; Yang et al., 2006). Once the best-fitting latent class model was determined, the likelihood of reporting each BPRS-E symptom was compared between the classes using Pearson's chi-square tests (X^2). To examine differences in diagnostic groupings (i.e. MAP and SZ), demographic, drug use, and clinical characteristics between the classes, Pearson's chi-square tests were used for categorical variables, and Kruskal–Wallis one-way analyses of variance were used for (non-normally distributed) continuous variables.

3. Results

3.1. Participant characteristics

The study sample consisted of 160 participants, with a median age of 39 years (interquartile range [IQR] = 33 – 46). The majority were male (66%), unemployed (68%) and single (66%). Participants had used methamphetamine for a median of 20.1 years (SD= 9.29), and 42% were currently dependent on the drug. During the previous month, participants had used methamphetamine on a median of 12 days (IQR = 5 – 20), with most reporting crystalline as the main form (93%) and injection as their main route of administration (76%). The majority of participants had also used tobacco (98%), cannabis (79%), and alcohol (65%) during the previous month. Half of the participants (50%) reported a family history of affective disorders and 32% reported a family history of SZ. Twenty participants (12%) met criteria for a lifetime DSM-IV diagnosis of SZ based on the CIDI. Seventy-eight participants (49%) met lifetime criteria for MAP (based on items from the CIDI).

3.2. Latent class analysis model

Indices of model fit were compared across two-class, three-class, and four-class models (Table 1). A five-class model was also estimated, but the results of this model were deemed unreliable, as the best log-likelihood was not replicated with 1000 random starts. Likelihood ratio tests indicated that goodness of fit was significantly improved with the inclusion of a second class (over a single-class model), and with the inclusion of a third class (over a two-class model). Goodness-of fit was not significantly improved with inclusion of a fourth class (over a three-class model). Relative to the four-class model, the three-class model had a higher AIC value, but a lower BIC value and a more parsimonious solution, with only modest decrease (3.5%) in entropy. The BIC has been

Table 1
Criteria for model selection in latent class analysis.

	Two-class model	Three-class model	Four-class model
AIC	2274	2240	2218
BIC	2388	2412	2449
Entropy	.833	.821	.856
Likelihood Ratio Tests (p-value)			
Voung-Lo-Mendell-Rubin	187.2 (p=.005)	72.5 (p=.001)	59.6 (p=.221)
Lo-Mendell-Rubin	185.3 (p=.005)	71.8 (p=.001)	59.0 (p=.226)

Note. AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion

recognised by several authors as a more reliable indicator of model fit (Nylundet al., 2007; Yang, 2006), and Raftery (1995) has argued that a model with a 10-point decrease in BIC value has a substantial (150:1) likelihood of being the more appropriate model. In consideration of all indices of model fit, and in particular the LRT comparisons and parsimony, the three-class model was selected as the best fitting model. Participants within the three classes were subsequently compared for their probability of reporting each BPRS-E symptom (Supplementary Table 2).

3.3. Latent symptom profiles

Class one comprised half of the participants (46%, *n*=74) and was labelled the 'low-pathology' class (Fig. 1). These participants reported a median of two clinically significant BPRS symptoms, most commonly anxiety and depression (50–59%), but had a much lower likelihood of positive psychotic symptoms (0–11%) compared with the other classes. Class two comprised one-third of participants (29%, *n*=46) and was labelled the 'moderate-pathology' class. These participants reported a median of five clinically significant BPRS symptoms, had a very high likelihood of most affective symptoms (depression, anxiety, and suicidality; 71–100%), and were more likely to report suspiciousness, hallucinations, and unusual thought content (22–46%) compared with people in the low-pathology class. Class three comprised one-quarter of participants (25%, *n*=40) and was labelled the 'high-pathology' class. Relative to people in other classes, those in the high-pathology class had a much higher likelihood of reporting all positive psychotic symptoms (32–82%), particularly unusual thought content (82%) and hallucinations (82%). These participants also experienced a much greater range of psychiatric symptoms relative to other classes. They reported a median of eight clinically significant BPRS symptoms, and were significantly more likely to experience tension (25%), conceptual disorganisation (20%), and all symptoms of activation (excitement, motor hyperactivity, distractibility; 15–20%), relative to people in other classes (0–3% reporting these symptoms).

3.4. Concordance with diagnostic constructs

Participants in the high-pathology class were significantly more likely to meet the lifetime diagnostic criteria for SZ (35%) than participants in the moderate-pathology class (7%). The remaining 58% of the high-pathology class did not meet criteria for either SZ or MAP (Table 2). Conversely, participants in the moderate-pathology class were significantly more likely to meet lifetime diagnostic criteria for MAP (72%) than participants in the high-pathology class (17%). Participants in the low pathology class were unlikely to meet criteria for SZ (4%) although 51% met the criteria for MAP.

3.5. Other correlates of class membership

Those in the high-pathology class were more likely to report a family history of SZ (47%) compared people in the moderate- (24%) or low-pathology classes (27%) (Table 2). Dependence on methamphetamine was more common in the moderate-pathology class (67%) than the low-pathology class (34%). Those in the high-pathology class were more likely to have nominated injection as their main route of methamphetamine administration during the past month (90%, *n*=36) relative to those in the low-pathology class (73%, *n*=54) and moderate-pathology class (70%, *n*=32).

4. Discussion

We identified three psychiatric symptom profiles among people who use methamphetamine, including two relatively distinct syndromes of psychotic symptoms (i.e. the moderate- and high-pathology profiles). These results are largely consistent with notion of a MAP syndrome that is phenotypically distinct from SZ. The moderate-pathology profile broadly aligns with current conceptualisations of methamphetamine-associated psychoses, with psychiatric symptoms (persecutory beliefs, hallucinations, and affective distress) that have been widely observed in MAP (McKetin et al., 2016; Voce et al., 2019a). Seventy percent of those with this profile met criteria for MAP during their lifetime, relative to 7% who met criteria for SZ. In contrast, the high-pathology profile broadly aligns with the current concept of SZ with comorbid methamphetamine use. Although the high-pathology profile was reported by a minority of methamphetamine users (25% of the total sample), it captured most (70%) of those who met criteria for SZ during their lifetime. By contrast, the high-pathology profile captured only 8% of people who met criteria for MAP during their lifetime. These people exhibited a higher propensity to currently experience delusions and hallucinations

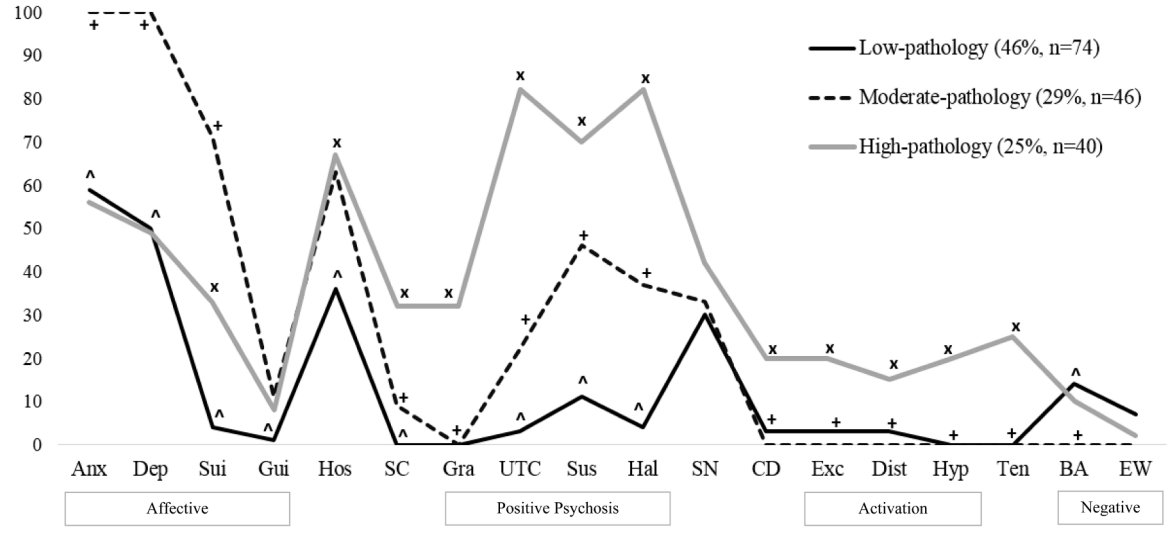


Fig. 1.. Probability of BPRS-E symptoms by class membership

Note. Symptoms include anxiety[(Anx)], depression[(Dep)], suicidality[(Sui)], guilt[(Gui)], hostility[(Hos)], somatic concern[(SC)], grandiosity[(Gra)], unusual thought content[(UTC)], suspiciousness[(Sus)], hallucinations[(Hal)], self-neglect[(SN)], conceptual disorganisation[(CD)], excitement[(Exc)], distractibility[(Dist)], hyperactivity[(Hyp)], tension[(Ten)], blunted affect[(BA)], and emotional withdrawal[(EW)]. Statistically significant differences in BPRS symptoms between latent classes is denoted with ^ (low- versus moderate-pathology), + (moderate- versus high-pathology), and x (low- versus high-pathology). Statistical comparison detailed in Supplementary Table 2.

Table 2
Demographic, clinical, and substance use characteristics by class membership.

	Low-pathology	Moderate-pathology	High-pathology	Test statistic (*p*-value)	Comparison between classes, X^2(*p*-value)		
					Low versus moderate	Moderate versus high	Low versus high
	(44%, *n*=74)	(31%, *n*=46)	(25%, *n*=40)				
Demographics and Clinical History							
Age in years, *mdn* (*IQR*)	39 (33 – 46)	38 (30 – 45)	41 (36 – 46)	3.3 (.199)	n/s		
Male sex, % (n)	74 (55)	50 (23)	67 (27)	7.5 (.023)	7.4 (.007)	2.7 (.101)	0.6 (.439)
Lifetime Schizophrenia Diagnosis, % (*n*)	4 (3)	7 (3)	35 (14)	24.1 (<.001)	0.4 (.551)	10.6 (.001)	19.0 (<.001)
Lifetime MAP[1], % (n)	51 (38)	72 (33)	17 (7)	25.6 (<.001)	4.9 (.027)	25.3 (<.001)	12.4 (<.001)
Family history affective disorder, % (*n*)	35 (26)	65 (30)	52 (21)	10.7 (.005)	10.3 (.001)	1.4 (.231)	3.2 (.072)
Family history of schizophrenia, % (*n*)	27 (20)	24 (11)	47 (19)	6.7 (.035)	0.1 (.705)	5.2 (.022)	4.8 (.028)
Methamphetamine Use							
Days of use in past month, *mdn* (*IQR*)	10 (4 – 20)	14 (6 – 21)	12 (6 – 21)	4.2 (.122)		n/s	
Dependence in past month, % (n)	34 (25)	67 (31)	52 (21)	13.2 (.001)	12.9 (<.001)	2.0 (.159)	3.8 (.052)
Age of first use, *mdn* (*IQR*)	18 (15 – 20)	18 (16 – 20)	18 (15 – 21)	0.1 (.981)		n/s	
Years of use, *mdn* (*IQR*)	21 (14 – 28)	17 (10 – 25)	23 (16 – 28)	3.7 (.155)		n/s	
Injection as main route of administration in past month[2], % (*n*)	73 (54)	70 (32)	90 (36)	5.7 (.056)	0.2 (.687)	5.4 (.020)	4.5 (.033)
Crystal as main form in past month[3], % (*n*)	95 (70)	91 (42)	92 (37)	0.51 (.774)		n/s	
Other Substance Use							
Cannabis use in past month[4], % (*n*)	80 (59)	76 (35)	82 (33)	0.5 (.760)	n/s		
Alcohol use in past month[5], % (*n*)	61 (45)	70 (32)	67 (27)	1.6 (.460)	n/s		
Tobacco use in past month[6], % (n)	97 (72)	96 (44)	100 (40)	1.68 (.431)	n/s		
Antipsychotic use in past month[7], % (n)	19 (14)	26 (12)	57 (23)	18.8 (<.001)	0.8 (.354)	8.7 (.003)	17.6 (<.001)

Note. *mdn* = median. *IQR* = interquartile range.
1. People with MAP were defined as having delusions or hallucinations that were considered to result from methamphetamine use among participants who did not meet criteria for SZ based on the Schizophrenia Module of the CIDI (Supplementary Table 1).
2. Other routes of administration include smoking (*n*=31), snorting (*n*=4), or swallowing (*n*=3) methamphetamine.
3. Other forms include powered (*n*=8), base (*n*=1), or prescription (*n*=2) methamphetamine.
4. No differences in days of cannabis use between the low- (*mdn* = 25), moderate- (*mdn* = 28), and high-pathology (*mdn* = 25) classes (F=0.30, p=.743).
5. No differences in days of alcohol use between the low- (*mdn* = 5), moderate- (*mdn* = 13), and high-pathology (*mdn* = 3) classes (F=1.67, p=.193).
6. No differences in days of tobacco use between the three classes (*mdn* = 28 across all classes) (F=2.19, p=.115).
7. Days of antipsychotic use was significantly higher among the high-pathology class (*mdn* = 28) relative to the moderate- and low-pathology classes (*mdn* = 1) (F=8.58, p=.005).

relative to people in the other classes and had a more extensive constellation of psychiatric symptoms (including conceptual disorganisation, tension, all symptoms of positive psychosis, and all activation symptoms). Of note, half of those in the low-pathology profile met lifetime criteria for MAP. It is possible that some of these people have a prior history of MAP but did not experience psychotic symptoms during the month preceding interview. Among chronic methamphetamine users, MAP is often a recurrent syndrome with episodes of psychotic symptoms followed by periods of recovery (Sato 1992; Sato 1986).

Our findings are consistent with experimental evidence demonstrating that exposure to amphetamines can exacerbate positive psychotic symptoms among people diagnosed with SZ (Curran et al., 2004). Other experimental studies, however, have shown a reduction in positive psychotic symptoms among people with SZ when exposed to amphetamine (Curran et al., 2004; van Kammen, 1982), suggesting that the role of dopamine in the pathophysiology of psychosis is complex and heterogenous (Hengartner & Moncrieff, 2018). Indeed, the neurobiological changes associated with heavy chronic methamphetamine use are more extensive and long-lasting than the changes that occur with acute methamphetamine intoxication (Ashok et al., 2017; Hsieh et al., 2014; Moszczynska, 2016).

Those with the high-pathology profile were significantly more likely to report a family history of psychosis, which is a well-documented risk factor for the development of SZ (Castle & Buckley, 2015). This may reflect a genetic predisposition that may make these individuals more vulnerable to developing a primary psychotic disorder (i.e. SZ), with psychotic symptoms precipitated or exacerbated by methamphetamine use. Kendler and colleagues (2019) found that people with MAP who transitioned to a diagnosis of SZ had the same elevated familial risk for psychosis as people with an initial diagnosis of SZ, concluding that SZ following MAP is better explained as a drug-precipitated disorder in vulnerable individuals rather than as a drug-induced syndrome. This conclusion also implies that not all forms of methamphetamine-related psychoses are a precipitation of SZ. Although not measured in the current study, it would be interesting to examine whether the moderate-pathology profile was associated with family history of drug abuse. Prior research indicates that familial risk scores for drug abuse are higher among people with MAP than methamphetamine users without psychosis (Kendler et al., 2019).

Our results support the clinical utility of retaining a separate diagnostic category for MAP. Differences in familial risk for psychosis associated with the moderate- and high-pathology profiles may correspond to unique aetiological mechanisms between the two syndromes. Nonetheless, we acknowledge the possibility that these latent profiles could represent divergent manifestations of a single disorder, given that different combinations of symptoms and risk factors can be observed among people who have the same clinical disorder (APA, 2013). Even so, the fundamental purpose of a diagnostic tool is to provide a useful framework for organising clinical phenomena, making inferences about likely outcomes, and guiding clinical decisions about treatment and management (Kendell, 1989). There are clinically meaningful differences between people with the moderate- and high-pathology profiles, with respect to their specific psychiatric and psychotic symptom profiles and levels of propensity for experiencing current psychotic symptoms. The moderate-pathology profile was reported by a non-trivial proportion of the methamphetamine-using population (29%), who have a comparatively lower propensity for psychotic symptoms (than people with the high-pathology profile) and primarily report persecutory delusions and hallucinations. These individuals could have different psychiatric comorbidities (i.e. higher rates of depression and anxiety) and may benefit from different treatment approaches (i.e. a focus on psychological rather than pharmacological therapies) relative to people in other classes. It is unlikely that such heterogeneity in psychosis would be adequately described under one single diagnostic category, in the case that MAP was subsumed under SZ as methamphetamine-precipitated SZ

(Bramness et al., 2012). Instead, retaining a discrete diagnostic category for MAP allows clinicians to identify and describe this clinically relevant subpopulation.

Whilst having a construct for MAP appears clinically useful, the existing diagnostic criteria may not provide a sufficiently reliable classification of this syndrome. Although the derived latent profiles show partial alignment with the diagnostic constructs of SZ and MAP, almost one-third of people with the moderate-pathology profile did not meet our criteria for MAP, and almost two-thirds of people in the high-pathology profile did not meet criteria for SZ. Moreover, half of those with the most extensive profile of psychiatric symptoms (high-pathology profile) did not meet criteria for either MAP or SZ. This lack of concordance between empirically-derived syndromes and the current diagnostic criteria may be due, in part, to poor sensitivity of the CIDI Schizophrenia module against the DSM-IV diagnosis of SZ compared with clinician ratings (Cooper et al., 1998). This discrepancy also supports criticisms that the existing diagnostic criteria for MAP have poor predictive validity and diagnostic stability (Mathias et al., 2008). Individuals diagnosed with MAP show substantial variability in their speed of recovery and tendency to relapse (Sato, 1992; Voce et al., 2019a; Yui et al., 2000), suggesting that the current diagnostic criteria do not reflect a homogeneous group. Attempts at refining these criteria could be guided by further data-driven analyses of people who use methamphetamine (such as LCA), which may clarify the novel boundaries between MAP and other conditions associated with psychotic symptoms. If applied to longitudinal data, future latent class analyses could identify whether certain classes (or syndromes) are associated with a greater risk of transitioning from MAP to SZ later in life, which may indicate clinical characteristics that more indicative of drug-precipitated SZ rather than a drug-induced psychosis.

Our results indicate that the presence of clinically significant conceptual disorganisation, tension, or activation symptoms, when combined with other patient information, could flag people who are more likely to meet diagnostic criteria for SZ. Almost half (45%) of those with the high-pathology profile reported at least one symptom of activation, tension, or conceptual disorganisation, compared with less than 7% of people in other classes. Individuals with these symptoms could benefit from early intervention from specialist psychosis services, particularly as disorganised symptoms are predictive of more unmet clinical and social needs (Derks et al., 2012) and generally poorer outcomes (Ortiz et al., 2017).

Negative symptoms are a recognised feature among some people with SZ, but are not listed in the symptom criteria for MAP (APA, 2013), leading some to argue that an absence of negative symptoms among people with MAP could be a point of distinction from SZ (Tomiyama, 1990). In the current study, clinically significant emotional withdrawal and motor retardation were uncommon across all three profiles. Accordingly, prior research indicates that only a minority of methamphetamine users with SZ (Srisurapanont et al., 2003; Srisurapanont et al., 2011) or MAP (Voce et al., 2019a) experience negative symptoms in psychiatric settings. Given the low prevalence of significant negative symptoms across community and psychiatric samples of methamphetamine users, observing negative symptoms may have limited practical utility for differentiating SZ and MAP. Moreover, recent evidence implies that negative symptoms among people with methamphetamine-related psychosis may be an artefact of sedative drug use, rather than forming a part of the MAP syndrome (Voce et al., 2019b).

4.1. Limitations and future research

There were several limitations to the current study. Our diagnosis of MAP was based on items from the Schizophrenia module of the CIDI, and this method of deriving a diagnosis of substance-induced psychosis has not been validated. Moreover, some individuals may have been incorrectly identified as not having SZ (false negatives), due to low sensitivity of the CIDI Schizophrenia module (Andrews & Peters, 1998). The CIDI Schizophrenia module is based on symptom criteria (criterion A) specified in the DSM-IV (APA, 1994), which has since been superseded by the DSM-5 (APA, 2013). In both editions, the presence of two or more symptom types is required to satisfy criterion A; however, in the DSM-IV, only one symptom type is needed if hallucinations contain commentary or third person conversations or delusions contain "bizarre" content. It is possible that fewer participants in the current study would have met criterion A for SZ if DSM-5 criteria were applied. Simiarly, participants with lifetime history of MAP were identified using a proxy measure (based on the DSM-IV criteria), rather than using a validated diagnostic tool. This catagorisation may have failed to detect all participants with a lifetime history of MAP, and these possible false negatives may explain why almost one-third of people with the moderate-pathology profile did not meet our criteria for MAP.

We did not identify participants with other primary psychotic disorders, such as bipolar disorder, and these individuals could have been captured under a diagnosis of SZ on the CIDI. The prevalence rate of comorbid methamphetamine use is higher among people with bipolar disorders, relative to people with other primary psychotic disorders (Grant et al., 2005; Estroff et al., 1985). As such, it would be informative for future research to explore how individuals with bipolar disorders are represented in latent psychiatric symptom profiles associated with past-month methamphetamine use. Likewise, participants were recruited from community settings, the symptoms profiles described here may not generalise to psychiatric in-patients with more severe and complex symptoms.

There are likely to be unmeasured factors that characterise certain latent classes, or confound the relationship between methamphetamine use and psychiatric symptoms, particularly with regard to patterns of substance use (e.g., dosage of methamphetamine used). Consistent with patterns of poly drug use widely observed among people who frequently use methamphetamine (Kelly et al., 2017), the current sample reported high rates of cannabis, tobacco, and alcohol use during the past month. Use of these drugs is associated with increased risk of psychotic symptoms, albeit the direction of causality remains debated (Auther et al., 2015; Gurillo et al., 2015; Marconi et al., 2016). Although recent rates of cannabis use, tobacco use, and alcohol use did not differ among the three derived classes, differences in lifetime exposure of these drugs may have influenced the psychiatric symptom profiles reported in this study. Likewise, participants were not asked about their most recent use of methamphetamine or the typical quantity of methamphetamine used. Without these measures, it is unclear to what extent the observed symptom profiles reflect different patterns of methamphetamine consumption (particularly those who use in a binging pattern of low frequency but high quantity) or subtle differences in intoxication levels during the interview. Antipsychotic medication use was more likely among those with the high-pathology profile (57%), relative to other profiles (19–26%), and may have attenuated positive psychotic symptoms or produced side effects (e.g. akathisia) that mimic tension, hyperactivity or negative symptoms (Caroff et al., 2011; Castle & Buckley, 2015; Lally & MacCabe, 2015).

Finally, future research may generate more precise and clinically useful demarcations between empirically-derived psychotic syndromes through the use of latent profile analysis. Whilst LCA derives groups based on whether individuals reported symptoms. Latent profile analysis (LPA) incorporates continuous (scale) data which may derive groups that are delineated by the severity level of psychiatric symptoms reported (Ferguson et al., 2020). Such an approach is consistent with a shift towards more dimensional approach to conceptualising mental disorders in psychiatry (Potuzak et al., 2012; van Os, 2014).

4.2. Conclusion

We identified two psychotic symptom profiles among people who use methamphetamine that aligned with diagnostic categories of MAP and

SZ, and a third symptom profile of depression and anxiety among people who did not report psychotic symptoms. These findings are consistent with the notion of a MAP syndrome that is clinically distinct from SZ, and suggest that the diagnostic construct of MAP has practical utility in allowing clinicians to draw inferences about psychosis liability, and guide symptom management among this population. A notable proportion of people who experienced psychotic symptoms were not captured in the diagnostic groupings of MAP or SZ, reflecting the many challenges involved in attempting to differentiate between these conditions using current diagnostic processes.

Statement of Author Contributions

Alexandra Voce generated the research question (35%), designed the analysis strategy (30%), analysed the data (70%), and wrote the manuscript (100%). Rebecca McKetin generated the research question (20%), designed the analysis strategy (20%), analysed the data (20%), and reviewed the manuscript (25%). Richard Burns generated the research question (15%), designed the analysis strategy (20%), analysed the data (10%), and reviewed the manuscript (25%). David Castle generated the research question (15%), designed the analysis strategy (15%), and reviewed the manuscript (25%). Bianca Calabria generated the research question (15%), designed the analysis strategy (15%), and reviewed the manuscript (25%).

Declaration of Competing Interest

All authors declare no actual or potential conflicts of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2021.113760.

References

Akindipe, T., Wilson, D., Stein, D., 2014. Psychiatric disorders in individuals with methamphetamine dependence: Prevalence and risk factors. Metabolic Brain Disease 29 (2), 351–357.

American Psychiatric Association, 2013. Diagnostic and statistical manual of mental disorders, 5th edn. American Psychiatric Association, Arlington, VA.

American Psychiatric Association, 1994. Diagnostic and statistical manual of mental disorders, 4th edn. American Psychiatric Association, Arlington, VA.

Andrews, G., Peters, L., 1998. The psychometric properties of the Composite International Diagnostic Interview. Soc. Psychiatry Psychiatr. Epidemiol. 33 (2), 80–88.

Arunogiri, S., Foulds, J., McKetin, R., Lubman, D., 2018. A systematic review of risk factors for methamphetamine-associated psychosis. Aust. N. Z. J. Psychiatry 52 (6), 514–529.

Ashok, A., Mizuno, Y., Volkow, N., Howes, O., 2017. Association of stimulant use with dopaminergic alterations in users of cocaine, amphetamine, or methamphetamine: A systematic review and meta-analysis. JAMA Psychiatry 74 (5), 511–519.

Auther, A., Cadenhead, K., Carrión, R., Addington, J., Bearden, C., Cannon, T., McGlashan, T., Perkins, D., Seidman, L., Tsuang, M., Walker, E., Woods, W., Cornblatt, B., 2015. Alcohol confounds relationship between cannabis misuse and psychosis conversion in a high-risk sample. Acta Psychiatr. Scand. 132 (1), 60–68.

Bell, D., 1965. Comparison of amphetamine psychosis and schizophrenia. Br. J. Psychiatry 111, 701–707.

Bramness, J., Gundersen, O., Guterstam, J., Rognli, E., Konstenius, M., Loberg, E., Medhus, S., Tanum, L., Franck, J., 2012. Amphetamine-induced psychosis–a separate diagnostic entity or primary psychosis triggered in the vulnerable? BMC Psychiatry 12, 221.

Caroff, S., Hurford, I., Janice Lybrand, J., Campbell, E., 2011. Movement disorders induced by antipsychotic drugs: implications of the CATIE schizophrenia trial. Neurologic Clinics 29 (1), 127–148.

Castle, D., Buckley, 2015. Schizophrenia, 2nd edn. Oxford University Press, Oxford, United Kingdom.

Castle, D., Jablensky, A., McGrath, J., Carr, V., Morgan, V., Waterreus, A., Valuri, G., Stain, H., McGuffin, P., Farmer, A., 2006. The diagnostic interview for psychoses (DIP): development, reliability and applications. Psychol. Med. 36, 69–80.

Chen, C., Lin, S., Sham, P., Ball, D., Loh, W., Murray, R., 2005. Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. Am. J. Med. Genet. B Neuropsychiatr. Genet. 136B (1), 87–91.

Cooper, L., Peters, L., Andrews, G., 1998. Validity of the composite international diagnostic interview (CIDI) psychosis module in a psychiatric setting. J. Psychiatric Res. 32, 361–368.

Curran, C., Byrappa, N., McBride, A., 2004. Stimulant psychosis: systematic review. Br. J. Psychiatry 185, 120–196.

Cuthbert, B, Insel, T., 2010. Toward new approaches to psychotic disorders: The NIMH Research Domain Criteria project. Schizophr. Bull. 36 (6), 1061–1062.

Darke, S., Ward, J., Hall, W., Heather, N., &Wodak, A. (1991). The opiate treatment index (OTI) researcher's manual. National drug and alcohol research centre technical report number 11. Sydney: National Drug and Alcohol Research Centre.

Dazzi, F., Shafer, A., Lauriola, M., 2016. Meta-analysis of the Brief Psychiatric Rating Scale - Expanded (BPRS-E) structure and arguments for a new version. J Psychiatr Res 81, 140–51.

Derks, E., Allardyce, J., Boks, M., Vermunt, J., Hijman, R., Ophoff, R., 2012. Kraepelin was right: A latent class analysis of symptom dimensions in patients and controls. Schizophr. Bull. 38, 495–505.

Estroff, T., Dackis, C., Gold, M., Pottash, A., 1985. Drug abuse and bipolar disorders. Int. J. Psychiatry Med. 15 (1), 37–40.

Ferguson, S., Moore, E., Hull, D., 2020. Finding latent groups in observed data: A primer on latent profile analysis in Mplus for applied researchers. Int. J. Behav. Dev. 44 (5), 458–468.

Flaum, M., Schultz, S., 1996. When does amphetamine-induced psychosis become schizophrenia? Am. J. Psychiatry 153 (6), 812–815.

Glasner-Edwards, S., Mooney, L., Marinelli-Casey, P., Hillhouse, M., Ang, A., Rawson, R., 2008. Methamphetamine Treatment Porject Corporate Authors. (2008). Clinical course and outcomes of methamphetamine-dependent adults with psychosis. J. Subst. Abuse Treat. 35 (4), 445–450.

Gossop, M., Darke, S., Griffiths, P., Hando, J., Powis, B., Hall, W., Strang, J., 1995. The severity of dependence scale (SDS): psychometric properties of the SDS in English and Australian samples of heroin, cocaine and amphetamine users. Addiction 90 (5), 607–614.

Grant, B., Stinson, F., Hasin, D., Dawson, D., Chou, S., Ruan, W., Huang, B., 2005. Prevalence, correlates, and comorbidity of bipolar I disorder and axis I and II disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. J. Clin. Psychiatry 66 (10), 1205–1215.

Grant, K., LeVan, T., Wells, S., Li, M., Stoltenberg, S., Gendelman, H., Carlo, G., Bevins, R., 2012. Methamphetamine-associated psychosis. J. Neuroimmune Pharmacol. 7 (1), 113–139.

Gurillo, P., Jauhar, S., Murray, R., MacCabe, J., 2015. Does tobacco use cause psychosis? Systematic review and meta-analysis. Lancet Psychiatry 2 (8), 718–725.

Hengartner, M., Moncrieff, J., 2018. Inconclusive evidence in support of the dopamine hypothesis of psychosis: Why neurobiological research must consider medication use, adjust for important confounders, choose stringent comparators, and use larger samples. Front. Psychiatry 9, 174.

Hsieh, J.H., Stein, D.J., Howells, F.M., 2014. The neurobiology of methamphetamine induced psychosis. Front. Hum. Neurosci. 8, 537.

Ikeda, M., Okahisa, Y., Aleksic, B., Won, M., Kondo, N., Naruse, N., et al., 2013. Evidence for shared genetic risk between methamphetamine-induced psychosis and schizophrenia. Neuropsychopharmacology 38 (10), 1864–1870.

Kelly, P., Robinson, L., Baker, A., Deane, F., McKetin, R., Hudson, S., Keane, C., 2017. Polysubstance use in treatment seekers who inject amphetamine: Drug use profiles, injecting practices and quality of life. Addict. Behav. 71, 25–30.

Kendell, R., 1989. Clinical validity. Psychol. Med. 19, 45–55.

Kendler, K., Ohlsson, H., Sundquist, J., Sundquist, K., 2019. Prediction of onset of substance-induced psychotic disorder and Its progression to schizophrenia in a Swedish national sample. Am. J. Psychiatry 176 (9), 711–719.

Kittirattanapaiboon, P., Mahatnirunkul, S., Booncharoen, H., Thummawomg, P., Dumrongchai, U., Chutha, W., 2010. Long-term outcomes in methamphetamine psychosis patients after first hospitalisation. Drug Alcohol. Rev. 29 (4), 456–461.

Lally, J., MacCabe, J., 2015. Antipsychotic medication in schizophrenia: a review. Br. Med. Bull. 114 (1), 169–179.

Landis, J., Koch, G., 1977. The measurement of observer agreement for categorical data. Biometrics 33, 159–174.

Lecomte, T., Dumais, A., Dugré, J., Potvin, S., 2018. The prevalence of substance-induced psychotic disorder in methamphetamine misusers: A meta-analysis. Psychiatry Res. 268, 189–192.

Lo, Y., Mendell, N., Rubin, D., 2001. Testing the number of components in a normal mixture. Biometrika 88 (3), 767–778.

Lukoff, D., Nuechterlein, K., Ventura, J., 1986. Manual for the expanded Brief Psychiatric Rating Scale. Schizophr. Bull. 12, 594–602.

Mathias, S., Lubman, D., Hides, L., 2008. Substance-induced psychosis: a diagnostic conundrum. J. Clin. Psychiatry 69 (3), 358–367.

Marconi, A., Di Forti, M., Lewis, C., Murray, R., Vassos, E., 2016. Meta-analysis of the association between the level of cannabis use and risk of psychosis. Schizophr. Bull. 42 (5), 1262–1269.

McKetin, R., Dawe, S., Burns, R., Hides, L., Kavanagh, D., Teesson, M., Young, M., Voce, A., 2016. The profile of psychiatric symptoms exacerbated by methamphetamine use. Drug Alcohol. Depend. 1 (161), 104–109.

McKetin, R., Voce, A., Burns, R., Ali, R., Lubman, D., Baker, A., Castle, D., 2018. Latent psychotic symptom profiles amongst people who use methamphetamine: what do they tell us about existing diagnostic categories? Front. Psychiatry 9, 578.

Medhus, S., Mordal, J., Holm, B., Morland, J., Bramness, J., 2013. A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. Psychiatry Res. 206 (1), 17–21.

Medhus, S, Rognli, E, Gossop, M, et al., 2015. Amphetamine-induced psychosis: Transition to schizophrenia and mortality in a small prospective sample. Am. J. Addict. 24 (7), 586–589.
Morris, S., Vaidyanathan, U., Cuthbert, B., 2016. Changing the diagnostic concept of schizophrenia: the NIMH research domain criteria initiative. In: Li, M, Spaulding, WD (Eds.), The Neuropsychopathology of Schizophrenia. Springer International Publishing, Cham, Switzerland, pp. 225–252.
Moszczynska, A., 2016. Neurobiology and clinical manifestations of methamphetamine neurotoxicity. The Psychiatric Times 33 (9), 16–18.
Muthén, M., 2012. MPLUS Version 7.2 [Computer Software. Muthén & Muthén, Los Angeles, CA.
by Muthén, B., 2004. Latent variable analysis: Growth mixture modeling and related techniques for longitudinal data. In: Kaplan, D. (Ed.), Handbook of quantitative methodology for the social sciences. Sage, Newbury Park, CA. byeditor.
Niemi-Pynttäri, J., Sund, R., Putkonen, H., Vorma, H., Wahlbeck, K., Pirkola, S., 2013. Substance-induced psychoses converting into schizophrenia: a register-based study of 18,478 Finnish inpatient cases. J. Clin. Psychiatry 74 (1), e94–e99.
Nylund-Gibson, K., Choi, A.Y., 2018. Ten frequently asked questions about latent class analysis. Transl. Issue Psychol. Sci. 4 (4), 440–461.
Nylund, K.L., Asparouhov, T., Muthén, B.O., 2007. Deciding on the number of classes in latent class analysis and growth mixture modeling: A monte carlo simulation study. Struct. Eq. Model. Multidiscipl. J. 14 (4), 535–569.
Ortiz, B., Gadelha, A., Higuchi, C., Noto, C., Medeiros, D., Pitta, J., de Araujo Filho, G., Hallak, J., Bressan, R., 2017. Disorganized symptoms predicted worse functioning outcome in schizophrenia patients with established illness. Clin. Schizophr. Relat. Psychoses 11 (3), 151–155.
Peralta, V., Cuesta, M., Giraldo, C., Cardenas, A., Gonzalez, F., 2002. Classifying psychotic disorders: issues regarding categorial vs. dimensional approaches and time frame to assess symptoms. Eur. Arch. Psychiatry Clin. Neurosci. 252 (1), 12–18.
Potuzak, M., Ravichandran, C., Lewandowski, K., Ongür, D., Cohen, B., 2012. Categorical vs dimensional classifications of psychotic disorders. Compr. Psychiatry 53 (8), 1118–1129.
Raftery, A.E., 1995. Bayesian model selection in social research. Soc. Method. 25, 111–164.
Sara, G., Large, M., Matheson, S., Burgess, P., Malhi, G., Whiteford, H., Hall, W., 2015. Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation. Aust. N. Z. J. Psychiatry 49 (2), 106–117.
Sato, M., 1992. A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. Ann. N. Y. Acad. Sci. 654, 160–170.
Sato, M., 1986. Acute exacerbation of methamphetamine psychosis and lasting dopaminergic supersensitivity–a clinical survey. Psychopharmacol. Bull. 22 (3), 751–756.
Srisurapanont, M., Ali, R., Marsden, J., Sunga, A., Wada, K., Monteiro, M., 2003. Psychotic symptoms in methamphetamine psychotic in-patients. Int. J. Neuropsychopharmacol. 6 (4), 347–352.
Srisurapanont, M., Arunpongpaisal, S., Wada, K., Marsden, J., Ali, R., Kongsakon, R., 2011. Comparisons of methamphetamine psychotic and schizophrenic symptoms: a differential item functioning analysis. Progress Neuro-Psychopharmacol. Biol. Psychiatry 35 (4), 959–964.
Tomiyama, G., 1990. Chronic schizophrenia-like states in methamphetamine psychosis. Jpn. J. Psychiatry Neurol. 44 (3), 531–539.
Topp, L., Mattick, R., 1997. Choosing a cut-off on the Severity of Dependence Scale (SDS) for amphetamine users. Addiction 92 (7), 839–845.
van Kammen, D., Bunney, W., Docherty, J., Marder, S., Ebert, M., Rosenblatt., J., Rayner, J, 1982. d-Amphetamine-induced heterogeneous changes in psychotic behavior in schizophrenia. Am. J. Psychiatry 139 (8).
van Os, J., 2014. The many continua of psychosis. JAMA Psychiatry 71, 985–986.
Ventura, J., Lukoff, D., Nuechterlein, K., Green, M., Shaner, A., Nuechterlein, K., Liberman, R., Green, M., Shaner, D., Lieberman, R., 1993. Brief Psychiatric Rating Scale Expanded Version (4.0) scales, anchor points, and administration manual. Int. J. Method Psychiat. Res. 3, 227–243.
Voce, A., Calabria, B., Burns, R., Castle, D., McKetin, R., 2019a. A systematic review of the symptom profile and course of methamphetamine associated psychosis. Substance Use & Misuse 54 (4), 549–559.
Voce, A., Burns, R., Castle, D., Calabria, B., McKetin, R., 2019b. Is there a discrete negative symptom syndrome in people who use methamphetamine? Comprehensive Psychiatry 93, 27–32.
Yang, C., 2006. Evaluating latent class analysis models in qualitative phenotype identification. Comput. Stat. Data Anal. 50 (4), 1090–1104.
Yui, K., Ishiguro, T., Goto, K., Ikemoto, S., 2000. Susceptibility to subsequent episodes in spontaneous recurrence of methamphetamine psychosis. Ann. N. Y. Acad. Sci. 914, 292–302.

Thesis Discussion

In the current thesis, I aimed to investigate the profile and underlying structure of psychotic symptoms among people who use methamphetamine, and to identify possible differences in the psychiatric symptom profiles of methamphetamine-associated psychoses (MAP) and schizophrenia (SZ). This aim was addressed in five research studies, with a focus on the use of data-driven techniques to provide a sophisticated understanding of the psychiatric symptom profile associated with methamphetamine use. The following chapter serves as an integrative overview of these five studies, in which I articulate the specific findings that pertain to each research question (Part A), and explore how these results relate to the diagnostic construct of MAP (Part B). I discuss possible implications for the diagnosis and clinical care of people with methamphetamine-related psychoses (Part C), and outline the main limitations of this thesis (Part D). Finally, I propose future research to build upon the current findings (Part E).

Part A: Findings for specific research questions

Research Question 1. Which psychiatric symptoms have been associated with MAP, and what is the typical duration of symptoms in MAP?

In study one, I present a systematic review of the published peer-reviewed literature into the profile and duration of psychiatric symptoms observed within MAP. The most consistently reported symptom was delusions of persecution (reported in 84% of studies), followed by auditory and visual hallucinations (65–69%). A wide range of other psychiatric symptoms was also commonly reported, including conceptual disorganisation, hostility, depression, and hyperactivity (28–53%). Less evidence was available for negative psychotic

symptoms, which were reported by a minority (fewer than 19%) of studies. A small body of longitudinal research suggested that negative symptoms might increase or stabilise over the course of MAP, whereas positive symptoms may reduce or stabilise over time. One-quarter of people with MAP experienced symptoms that persisted beyond one month after acute intoxication.

Persecutory ideation, referential delusions, hallucinations, hyperactivity and hostility were prominent among people with MAP, which reflects the profile of symptoms described in early experimental studies of the syndrome (37, 40, 44, 107, 109, 110). These findings also align with the factor structure of methamphetamine-exacerbated symptoms reported by McKetin and colleagues (40), which included positive psychotic symptoms, affective symptoms (i.e. depression), as well as symptoms of psychomotor agitation (i.e. hyperactivity). This review demonstrates that the profile and duration of MAP symptoms vary across studies with differing research methodologies (i.e. differences in study designs, gender of participants, recruitment sources, and geographic locations). For instance, cases of persistent MAP were more commonly reported among studies conducted in Japan (relative to studies conducted elsewhere). Negative symptoms were more commonly reported among samples recruited from psychiatric (relative to community) settings, and among samples in which a majority of participants were male (relative to samples with mostly female participants).

Research Question 2. What is the association between methamphetamine use and psychiatric symptoms in people with primary psychotic disorders, specifically schizophrenia or affective psychoses?

In study two, I presented novel evidence that illicit methamphetamine use is linked to a higher likelihood of positive psychotic symptoms among a community-based sample of

people with primary psychotic disorders. Among people with SZ, those who had used methamphetamine in the past year were significantly more likely to report hallucinations, persecutory delusions, symptoms of depression, and racing thoughts compared to people with SZ who did not use methamphetamine in the past year. These findings are consistent with experimental research showing that prescription amphetamines can exacerbate existing psychotic symptoms, and precipitate the onset of new symptoms, among people with SZ in controlled laboratory settings (75). An equivalent association between methamphetamine use and positive psychotic symptoms was not found for people with affective psychotic disorders. However, people with affective psychoses who had used methamphetamine in the past year were (marginally) more likely to report manic symptoms (i.e. reckless activity, inappropriate social behaviour, and racing thoughts) compared to those without past-year methamphetamine use (18). Although these findings require replication with a larger sample, they are consistent with prior research suggesting that stimulant pharmacotherapy is linked to an increased risk of hospitalisation for mania among people with bipolar disorder (117).

Research Question 3. What is the underlying factor structure of psychiatric symptoms in people who use methamphetamine (but do not have SZ)?

In study three, exploratory factor analysis was used to identify three latent factors underlying the profile of current psychiatric symptoms among people who use methamphetamine. The first "positive-activation" factor (comprised of delusions, hallucinations, conceptual disorganisation, and symptoms of activation) was positively associated with the second "affect" factor (i.e. depression, anxiety, and hostility), but negatively associated with the third "negative symptoms" factor (i.e. blunted affect, emotional withdrawal, and motor retardation). This negative symptom factor was identified in one-third of people who use methamphetamine, and this syndrome manifested in a different latent class of methamphetamine users from those people who manifested positive

symptoms. Moreover, this negative syndrome was unrelated to methamphetamine use or dependence (unlike the positive-activation syndrome) but was associated with use of heroin and benzodiazepines.

In this study, I identified an empirically-derived negative syndrome among people who use methamphetamine, and specifically examined the relationship between this syndrome and methamphetamine use. Although negative symptoms have been reported in a minority of studies into MAP, it has previously been unclear whether these symptoms are attributable to methamphetamine use or to confounding factors (40, 45). The results of this study suggest that negative symptoms in this population do not occur as a component of the MAP syndrome, but rather, as an artefact of polysubstance use (specifically the use of central nervous system depressants that can produce secondary negative symptoms (111-114)). This interpretation is synergistic with the findings of McKetin and colleagues (40, 45), who found that methamphetamine use was not associated with an exacerbation (or increase) in negative symptoms. They also reconcile the findings of Srisurapanont and colleagues (40, 45), who identified a negative syndrome in MAP but did not examine the association between this syndrome and methamphetamine use. This interpretation is also consistent with the observation that stimulant use is associated with worsened positive, but not negative, psychotic symptoms among people with SZ (115) and people with methamphetamine-related psychosis (116).

Research Question 4. Are there different profiles of lifetime delusions and hallucinations among people who use methamphetamine, and how do these positive psychosis profiles correspond to the diagnostic criteria for SZ?

Using latent class analysis (study four), I identified three profiles (or syndromes) of positive psychotic symptoms among people who used methamphetamine, and explored how these profiles corresponded to the diagnostic construct of SZ. These profiles represented different subpopulations of people, who varied in their lifetime profiles of specific delusions and hallucinations, their likelihood of meeting criteria for SZ, and their propensity to experience psychotic symptoms during their lifetime. A minority of people (represented in the *schizophrenia-like* profile) were significantly more likely to meet criteria for SZ (26% cf. 0–3%) and had a higher likelihood of reporting almost every type of hallucination and delusion (including more complex auditory hallucinations and non-persecutory delusions) relative to other methamphetamine users. Over half of the participants (represented in the *paranoid psychosis* profile) reported persecutory delusions, visual hallucinations, and auditory hallucinations, but at a lower probability than those in the *schizophrenia-like* profile. One-fifth of people (represented in the *few symptoms* profile) exhibited comparatively low levels of positive symptoms, with the exception of one-third who experienced persecutory ideation. Very few individuals in the *paranoid psychosis* profile met criteria for SZ (3%), suggesting that the heterogeneity in lifetime psychotic symptoms among people who use methamphetamine is not sufficiently captured under this single diagnostic category (SZ).

Research Question 5. Are there different profiles of current psychiatric symptoms among people who use methamphetamine, and how do these profiles represent people with SZ and people with MAP?

Using latent class analysis (study five), I identified three profiles (or syndromes) of current positive, affective, and activation/disorganised symptoms among people who use methamphetamine. The subpopulations represented in these discrete profiles reported different specific psychiatric symptoms, and had discrepant likelihoods of experiencing current psychotic symptoms. Half of the population (represented in a *low-pathology* profile)

had a low likelihood of reporting any psychotic symptoms (hallucinations, suspiciousness, grandiosity, unusual thought content; 0–11%). One-third of people (represented in a *moderate-pathology* profile) reported suspiciousness and hallucinations (37–46%), and were significantly more likely to meet criteria for MAP (70%) compared to other profiles (15–51%). A minority of people (represented in a *high-pathology* profile) had a much higher likelihood of experiencing every symptom of positive psychosis (suspiciousness, hallucinations, grandiosity, unusual thought content; 32–82%) and reported a much broader range of psychiatric symptoms (including tension, conceptual disorganisation, and activation). Those with the *high-pathology* profile were also significantly more likely to meet criteria for SZ (35%) compared to people with other profiles (4–7%). This data-driven analysis provides novel evidence that people who meet criteria for MAP are typically represented in a different latent psychiatric symptom profile from people who meet criteria for SZ.

Part B: The diagnostic construct of methamphetamine-associated psychosis (MAP)

A major question within the published literature is whether MAP should be conceptualised as a distinct disorder or as a precipitation of SZ (108). In current classification systems for psychotic disorders, MAP is considered a separate condition from primary psychotic disorders. Compelling experimental evidence supports the existence of a drug-induced psychosis that is attributable, and temporally linked, to methamphetamine use (36, 37). However, MAP and SZ share similar profiles of psychiatric symptoms, longitudinal courses, genetic and environmental risk factors (45, 84, 118), leading some to propose that these conditions constitute one clinical entity. Bramness and colleagues (108) argue that

methamphetamine use acts as an environmental trigger to precipitate SZ in people with an underlying vulnerability to the disorder. This viewpoint raises the question of whether assigning people to non-overlapping diagnostic categories of MAP or SZ oversimplifies the diagnostic process by imposing artificial boundaries between these disorders. In the following section, I discuss how each major finding of the current research might align with a categorical perspective (i.e. MAP as separate from SZ) or dimensional perspective (i.e. MAP as a form of SZ).

Negative symptoms

The current research suggests that negative symptoms could be a point of differentiation between people with SZ and MAP. Negative psychotic symptoms are featured within the symptom criteria for SZ (although not requisite for a diagnosis) and are observed in approximately one-quarter of people with SZ (80). The findings of study three indicate that negative symptoms may occur as an artefact of polysubstance use among people without SZ, and although a formal diagnosis of MAP was not made among this sample, these results support the assertion that negative symptoms are not a core component of the MAP syndrome (40). This implies that MAP may be associated with a different symptom profile from SZ – consistent with viewpoint of MAP as a distinct clinical entity. Prior research indicates that negative symptoms are associated with different genetic variations, pathways of neural activation, and neurocognitive impairments to positive symptoms of psychosis (119, 120). Thus, the expression of primary negative symptoms in SZ (and not MAP) could reflect distinct neurobiological or genetic underpinnings between these two disorders, although further research is needed to test this possibility.

The possible role of dopamine

The current findings align with the notion that dopaminergic dysregulation is a shared mechanism underlying both MAP and SZ. Methamphetamine exposure prompts the release of dopamine (2, 4), and according to the dopamine hypothesis of psychosis, an overabundance of dopamine plays a causal role in the expression of positive psychotic symptoms (61). In study three, positive-activation symptoms (e.g. suspiciousness, hallucinations) were associated with methamphetamine use and dependence among people who did not meet criteria for SZ. In study two, methamphetamine use was associated with hallucinations and persecutory delusions among people with SZ, but importantly, methamphetamine use was not associated with positive psychotic symptoms among people with affective psychotic disorders. This latter finding implies that methamphetamine use increases risk of psychosis by acting on pathways that are specific to both SZ and MAP, consistent with the perspective that these disorders constitute a common clinical entity. Nonetheless, many related disorders share overlapping neural underpinnings (18); for instance, several studies have demonstrated that hyperactivation of the amygdala is common across all types of anxiety disorders (121). Thus, evidence of a shared neural (i.e. dopamine) dysfunction also does not preclude the possibility that MAP and SZ represent two discrete disorders.

Separate syndromes of psychosis

In the current research, I identified two psychotic syndromes underlying the lifetime and current symptom profiles of people who use methamphetamine; a syndrome characterised by paranoia and hallucinations (*paranoid psychosis profile* in study four; *moderate-pathology profile* in study five) differentiated from a syndrome of multiple types of delusions and complex hallucinations (*schizophrenia-like profile* in study four, *high-pathology profile* in study five). Importantly, these two syndromes were not associated with differences in methamphetamine use, but they were associated a differential likelihood of

experiencing delusions and hallucinations (which was significantly higher among those in the *high-pathology* and *schizophrenia-like profile*s relative to those in the *paranoid psychosis* and *moderate-pathology profiles)*. From a dimensional perspective, it could be argued that these empirically-derived syndromes represent different manifestations (i.e. differing severities) of the same psychotic illness, with individuals further along the continuum of psychosis (i.e. *schizophrenia like* and *high-pathology profiles*) reporting a higher likelihood of symptoms relative to those at milder ends of the continuum. However, these syndromes were also characterised by differences in the specific type of psychotic symptoms reported. In study four, people with the *schizophrenia-like* profile were substantially more likely to report non-persecutory delusions and complex auditory hallucinations relative to those with the *paranoid psychosis* profile. In study five, those with the *high-pathology* profile were substantially more likely to report symptoms of activation, tension, conceptual disorganisation, and unusual thought content (i.e. non-persecutory delusions) relative to the *moderate-pathology* profile. These differences in type imply that these syndromes are not simply different severities of the same disorder, but rather, they reflect distinct illnesses.

These two empirically-derived syndromes align with current diagnostic classifications of MAP and SZ, consistent with a categorical perspective that these disorders are separate clinical entities (18). Current conceptualisations of MAP are broadly reflected in the *paranoid psychosis* and *moderate-pathology* profiles, which were characterised by a symptom profile (paranoia, hallucinations, and affective distress) widely observed in MAP (40, 122). These profiles captured only a small proportion (3–7%) of people who met criteria for SZ, and in study five, 70% of people with the *moderate-pathology* profile met criteria for MAP. In contrast, current conceptualisations of SZ with comorbid methamphetamine use broadly align with the *schizophrenia-like* and *high-pathology* profiles, which captured a majority of people who met criteria for SZ (65–70%). In study five, individuals with the

high-pathology profile were significantly more likely to report a family history of psychosis (reported by 47%), which is a well-documented risk factor for the development of SZ (48). This likely reflects an underlying predisposition that makes these people more vulnerable to developing SZ precipitated or exacerbated by methamphetamine use. Kendler and colleagues (123) found that people with MAP who transitioned to a diagnosis of SZ had the same elevated familial risk for psychosis as people with an initial diagnosis of SZ, concluding that SZ following MAP is better explained as a drug-precipitated disorder in vulnerable individuals rather than a drug-induced syndrome. This conclusion implies that not all forms of methamphetamine-related psychoses are a precipitation of SZ, and methamphetamine-induced psychoses exist separate from SZ.

The demonstration of two discrete psychotic syndromes among people who use methamphetamine is largely consistent with the notion that the MAP syndrome is a distinct clinical entity from SZ. However, this finding does not preclude the possibility that these syndromes represent different severities along one continuum of psychotic disorder, in line with a dimensional perspective of MAP as a precipitation of SZ (108). This model is based on a diathesis-stress model of psychiatric disorders (124), in which liability to psychosis is attributed to a combination of environmental stressors (i.e. methamphetamine use, trauma, socio-economic challenges) and dispositional vulnerability (i.e. genetic risk). It is hypothesised that a low level of methamphetamine use is needed to trigger a psychotic episode for someone with high vulnerability to SZ, whereas an extreme level of methamphetamine exposure is required to catalyse a psychotic episode for someone with a lower dispositional vulnerability. Accordingly, people with the *high-pathology* or *schizophrenia-like* profiles may have experienced a more severe profile of psychotic symptoms, without requiring a greater level of methamphetamine exposure, because they

have a greater latent vulnerability to psychosis (i.e. familial risk) compared to other people who used methamphetamine.

Within schizophrenia, many authors have speculated about different "clinical forms" or "subtypes" comprising different profiles of psychiatric symptoms, functional impairments, and biological correlates. Castle and colleagues (174) applied latent class analysis to 447 first contact patients with a diagnosis of schizophrenia, and found evidence for a neurodevelopmental subtype (characterised by early onset, restricted affect, poor pre-morbid adjustment, and male sex), a paranoid subtype (characterised by later onset, persecutory delusions), and a schizoaffective subtype (characterised by dysphoria, persecutory delusions, and female sex). Thus, it is possible that the two psychotic syndromes derived in the current latent class analyses reflect different symptoms profiles among people with schizophrenia. This is consistent with prior cluster analysis studies (156, 176) that have described a subset of people diagnosed with schizophrenia who predominately report delusions and hallucinations (as observed in the moderate-pathology profile).

Interestingly, the *low-pathology* profile was characterised by a lower likelihood of current psychotic symptoms relative to the *moderate-pathology* profile, even though these two profiles were associated with comparable rates of family history of SZ (24–27%). This may reflect an interaction between genetic vulnerability and methamphetamine use, as people with the *moderate-pathology* profile were significantly more likely to be dependent on methamphetamine (67% cf. 34%), in line with recent evidence indicating that severe substance use is a risk factor for MAP (125). Whilst this thesis cannot provide definitive evidence on the validity of a categorical or dimensional approach for conceptualising the relationship between MAP and SZ, the current results are nonetheless consistent with the need for a diagnostic category of MAP.

Clinical Utility

There is clinical utility in retaining a diagnostic category for MAP separate from SZ. MAP and SZ are constructs within a classification system, which ultimately aims to provide clinicians with a useful framework for organising psychotic phenomena, to guide decisions about treatment and to facilitate inferences about individual outcomes (18, 126, 127). In psychiatry, artificial boundaries may be constructed around continuous phenomena to allow clinicians to make categorical decisions, for example, by defining a cut-off point for symptoms that are of "clinically significant" severity to warrant treatment (18, 128).

The two conceptually distinct syndromes of psychosis derived in the current thesis involved different symptom profiles, risk factor correlates (i.e. familial history of psychosis), and levels of likelihood for experiencing psychosis. It is unlikely that this heterogeneity in psychosis would be accurately or reliably captured under a single diagnostic category, if the concept of MAP was subsumed under SZ (as SZ precipitated by methamphetamine use). Instead, having a category for MAP allows clinicians and researchers to identify and categorise the distinct subpopulation of people (i.e. those with the *paranoid psychosis* and *moderate-pathology* profiles) who report persecutory delusions and hallucinations, have lower familial risk for psychosis, and a lower propensity to experience psychotic symptoms (relative to those with the *schizophrenia-like* and *high-pathology* profiles). These individuals constitute a substantial proportion of the methamphetamine-using population, and – although not tested in the current thesis – they likely differ from other methamphetamine users in regard to their episode duration, prognosis, comorbidity with other psychiatric conditions, and responsiveness to different treatments (e.g. may be less likely to require long-term antipsychotic medication).

As emphasised by several authors (129-131), categorical and dimensional perspectives are not mutually exclusive approaches of conceptualising psychiatric disorders, and could be useful for different tasks. A categorical distinction between SZ and MAP may be more practical for statistical reporting on prevalence and outcomes for MAP, for facilitating clinician decision-making (i.e. whether to treatment is necessary), and for aiding effective communication between patients, clinicians, and the community. Conversely, dimensional approaches may be more precise when investigating the neurobiological basis of these psychotic disorders (132).

The MAP diagnostic criteria

Although retaining a diagnostic category for MAP may be clinically useful, it appears that this syndrome is not sufficiently defined within the existing DSM criteria. In study five, although the *moderate-pathology* profile broadly aligned with the diagnostic concept of MAP, one-third of people with this profile did not meet criteria for MAP. This lack of concordance between the empirically-derived syndromes and the current diagnostic criteria supports criticisms that the existing DSM criteria (18) do not provide an accurate or reliable definition of the MAP syndrome (65, 198). This argument reflects the observation that people diagnosed with MAP demonstrate substantial variability in the course and long-term outcomes of their condition. Diagnoses based on the existing criteria tend to have poor diagnostic stability (65), as a notable proportion of people (16 – 39%; 123, 133-135) initially diagnosed with MAP are eventually re-diagnosed with SZ later in life. This variability in outcome could suggest that the current criteria do not capture a homogeneous group.

Alternatively, poor concordance between the diagnostic construct for MAP and the observed latent symptom profiles may reflect inaccuracies in the diagnostic classifications used within the current research. Lifetime DSM-IV diagnoses of SZ made using the CIDI

schizophrenia module have adequate sensitivity (68–93%) and specificity (50-95%) against diagnostic ratings made by experienced clinicians (for SZ criteria A, B, D, E, F) (136). However, this module has very low sensitivity (20%) for SZ criteria relating to symptom duration (criteria C), meaning that some individuals with SZ may not have been accurately identified. This would explain why most individuals in the *schizophrenia-like* profile did not meet the diagnostic criteria for SZ (based on the CIDI), despite this profile capturing most people who did meet these criteria. Likewise, some people with the *moderate-pathology* profile who did not meet criteria for MAP may have had undetected SZ.

The discrepancy between our empirically-derived psychotic syndromes and the current diagnostic categories is consistent with a major criticism of the categorical approach to diagnostic classification –that patients with the same psychiatric disorder diagnosis often present with different symptom profiles (177). Those with schizophrenia can present with different profiles of psychiatric symptoms, functional impairments, and biological correlates, leading many authors to speculate about different "clinical forms" or "subtypes" of the disorder (178). Using latent class analysis, Castle and colleagues (174) identified three subtypes of patients diagnosed with schizophrenia, including a neurodevelopmental subtype (characterised by early onset, restricted affect, poor pre-morbid adjustment, and male sex), a paranoid subtype (characterised by later onset, persecutory delusions), and a schizoaffective subtype (characterised by dysphoria, persecutory delusions, and female sex). It is possible that the two psychotic syndromes derived in the current latent class analyses reflect different symptoms profiles associated with schizophrenia (rather than separate profiles for MAP and SZ). This is consistent with prior cluster analyses (156, 176) that have described a subset of people diagnosed with schizophrenia who predominately report delusions and hallucinations (as observed in the moderate-pathology profile).

The poor alignment between our empirically-derived psychotic syndromes and the current diagnostic categories is also consistent with a second major criticism of the categorical approach to diagnostic classification – the lack of specificity observed between diagnostic groupings. More specifically, patients with different diagnoses often share similar psychiatric symptoms and signs, and overlapping neurobiological and genetic correlates. Bipolar disorder, schizophrenia, and MAP all share overlapping psychiatric symptoms (e.g. paranoia, grandiosity, auditory hallucinations, agitated behaviour, suicidality), genetic and environmental risk factors (i.e. family history of psychosis, childhood trauma), and neurobiological similarities (i.e. dopamine abnormalities) (179, 180). Within the current latent class models, it is possible that people with MAP and SZ were represented in both psychotic symptom profiles. Although the high-pathology profile represented most individuals who met criteria for SZ (70%), it also captured 15 percent of those with a diagnosis of MAP. Conversely, the moderate-pathology profile represented most of those who met criteria for MAP (70%); it also represented 7 percent of those with SZ. Some authors (181) contend that psychiatric has not identified any single set of symptoms, signs, or tests to reliably delineate psychiatric disorders (including MAP from SZ) into fully discrete categories. This limitation has prompted many to argue that categorical boundaries between psychotic disorders do not reflect the true nature of psychiatric diseases, which are better conceptualised as existing on a dimension or continuum (or many continua). From this perspective, it could be argued that these empirically-derived syndromes represent different manifestations (i.e. differing severities) of the same psychotic illness (SZ), with individuals further along the continuum of psychosis reporting a higher likelihood of symptoms relative to those at milder ends of the continuum (83).

Indeed, the current diagnostic categories are unlikely to perfectly represent the true underlying nature of psychotic disorders. Kendler (182) speculates that psychotic disorders

involve unique webs of interrelated symptoms, signs, and underlying pathophysiology that are separated by "fuzzy boundaries". Even if psychotic phenomena are dimensional in nature, Kendler (182) argues that it may be useful for clinicians to construct artificial boundaries around these continuous phenomena to allow clinicians to make categorical decisions.

Part D: Implications for diagnosis and intervention

Polysubstance use was associated with negative symptoms among people who use methamphetamine in the current research. Methamphetamine is often used concurrently with other drugs (23, 137), including heroin and benzodiazepines. As negative symptoms are listed within the diagnostic criteria for SZ (18), overlooking the role of polysubstance use in secondary negative symptoms may lead to a misdiagnosis of SZ among people with methamphetamine-related psychoses. These findings highlight the need for clinicians to assess each patient's lifetime history of drug use across all classes of licit and illicit substances, including the drug types used, recent changes in drug use patterns, and the timing and quantity of most recent use for each drug type. Taking self-reported histories of drug use may be difficult in some clinical settings, particularly when an individual is experiencing an acute psychotic episode and may be disorientated or uncooperative. Nonetheless, these assessments would help to ensure that people with MAP receive an accurate diagnosis and appropriate treatment plan, with a focus on the management of substance use rather than the long-term provision of antipsychotic medications.

A large subset of people who use methamphetamine will experience psychotic symptoms (particularly paranoia) without reaching the clinical threshold for a psychotic disorder. Despite not meeting the full criteria for a clinical disorder, these symptoms may still cause distress and impairment, and if left untreated, may lead to the development of more

serious and enduring psychotic episodes (67). The prominence of persecutory ideation in the methamphetamine-using population may have serious consequences for the individual and the broader community, particularly with regard to aggressive behaviour, as some people may act violently as a pre-emptive defence against misperceived threats (138, 139). Public education strategies may assist people who use methamphetamine to recognise persecutory ideas in themselves and their peers, and encourage them to contact relevant mental health services for further evaluation and treatment. Law enforcement, emergency medical staff, and families of people who use methamphetamine may also benefit from similar education on how to respond appropriately to delusional or aggressive behaviour associated with methamphetamine intoxication (140).

The findings of this thesis demonstrate that many people experience psychotic symptoms without meeting criteria for MAP and SZ. This further demonstrates that delusions and hallucinations do not always occur in the context of a psychotic disorder, and are not always associated with distress or impairment. This aligns with a recent meta-analysis indicates that 6 percent of the general population experience hallucinatory or delusional experiences in their lifetime, without having a clinical psychotic disorder (McGrath et al., 2015). This highlights the need to dispel the commonly-held misconception among general public and health care professionals (141) that psychotic experiences are indicative of a serious psychotic disorder and poor outcomes. Such misconceptions can create internalised stigma, fear and anxiety among people who experience psychotic symptoms, which in turn, can prevent people from disclosing distressing symptoms to others (142). Public education campaigns play an important role in demystifying and destigmatising psychosis, and encouraging help-seeking among those who need support (143).

Specific types of psychotic symptoms may flag methamphetamine users who are more likely to have an underlying psychotic disorder. The *schizophrenia-like* profile (in

study four) was characterised by a lifetime history of complex auditory hallucinations and non-persecutory delusions (e.g. thought interference, passivity, or projection). The *high-pathology* profile (in study five) was characterised by current symptoms of activation (distractibility, excitement/emotional lability, hyperactivity), tension, and conceptual disorganisation (i.e. confused, vague, or disconnected speech). These symptoms were associated with a higher likelihood of meeting diagnostic criteria for SZ. In clinical settings, the presence of these symptoms could flag methamphetamine users who may be greater risk of having an underlying psychotic disorder, and who might benefit from early intervention from specialist psychosis services to monitor psychotic symptoms over long-term.

Anxiety and depression often co-occur with psychotic symptoms among people who use methamphetamine. Affective symptoms (particularly suicidality, anxiety, and depression) constitute a latent factor underlying the profile of current psychiatric symptoms among people who use methamphetamine, and these affective symptoms are positively associated with methamphetamine use and positive psychotic symptoms (study three). Likewise, one-third of studies into the symptom profile of MAP report depression and anxiety (study one). This aligns with evidence indicating that depression and anxiety can precipitate positive psychotic symptoms in the general population (143), which suggests that affective symptoms worsen delusions and hallucinations in some people who use methamphetamine. Managing depression and anxiety may help some people to reduce methamphetamine use by alleviating the need to self-medicate (144), which in turn, would likely improve psychotic symptoms. Because people are more likely to seek treatment for depression or anxiety compared to symptoms of psychosis (145), likely due to the stigma associated with psychotic disorders, healthcare providers should screen for delusions and hallucinations among people who use methamphetamine and report affective disturbances.

Illicit methamphetamine use is linked to symptoms of psychosis and depression among people with SZ (study two). This relationship may underlie the poorer treatment response and overall worse prognosis observed in dual diagnosis patients with both psychotic and methamphetamine use disorders (146-148). Given that the lifetime rate of stimulant use disorders is considerably higher for people with SZ (9%) relative to the general Australian population (3%) (68), people with SZ should be informed that methamphetamine use may worsen their symptoms. People who have both SZ and substance dependence should also receive treatment that holistically addresses both these comorbidities (149).

Part E: Limitations

The aforementioned implications must be placed in the context of several caveats. Each individual study in this thesis included a statement of the main limitations of the specific dataset used; as such, the following section addresses broader limitations that are applicable across multiple studies within this thesis. First, this research measured the relationship between methamphetamine use and psychotic symptoms among people recruited from the community. The systematic review presented in study one (122) found that most research into MAP has relied on in-patients recruited from psychiatric or emergency departments, and these samples tend to report more disorganised and negative psychotic symptoms relative to samples drawn from community settings. Prior research demonstrates that clinical samples of methamphetamine users tend to report more co-morbid psychiatric issues, heavier methamphetamine use, and more severe rates of methamphetamine dependence (150). As such, the symptom profiles reported in the current research may not generalise to psychiatric in-patients with more severe and complex symptoms. In particular, the current research could not examine the correlates of specific negative symptoms due to

low endorsement of negative symptom items among the respondents. Potuzak and colleagues (131) caution against evaluating only severe hospitalised patients when studying psychotic disorders, as this evidence must be complemented with community-based samples to understand the full spectrum of psychotic symptomatology. This thesis captures a community-based population that has been underrepresented in literature, and when combined with research from in-patient samples, the current findings provide a more holistic and ecologically valid representation of the various psychiatric symptom profiles associated with methamphetamine use.

Second, other confounding factors associated with both methamphetamine use and psychosis were not measured in the current research. Substance use disorders and psychotic disorders are both associated with common genetic factors, indicators of cognitive dysfunction and neurobiological abnormalities (149, 151), and environmental stressors, including socio-economic inequality, poverty, social isolation, childhood abuse, and other traumatic life events (149, 151). Inclusion of these factors would be particularly important for future research that adopts a diathesis-stress perspective of psychosis among this population. Similarly, there was a high rate of polysubstance use in this sample, particularly with regard to cannabis, which has been consistently recognised as the most common secondary illicit substance used by frequent methamphetamine users (152). Cannabis use is associated with an increased risk of developing a psychotic disorder (153), and concurrent use of cannabis and methamphetamine linked to greater neurocognitive impairment than methamphetamine use alone (154). Although most analyses were adjusted for recent cannabis use, differences in lifetime patterns of cannabis use may have influenced the psychiatric symptom profiles reported in this research.

The use of the CIDI schizophrenia module to diagnose SZ is a key limitation of the current research. First, this module is based on symptom criteria (criterion A) specified in the

DSM-IV (166), which has since been superseded by the DSM-5 (18). In the DSM-IV diagnostic criteria for SZ, certain types of delusions (i.e. those containing "bizarre" content) and hallucinations (i.e. those involving a running commentary or multiple voices conversing) were considered diagnostically significant, and the presence of one such symptom was sufficient to satisfy criterion A. This emphasis has since been removed in the DSM-5 criteria for SZ, which requires the presence of two or more symptom types to satisfy criterion A (regardless of delusional or hallucinatory content). Thus, fewer participants in the current study may have met criterion A for SZ if DSM-5 criteria were applied. Second, the CIDI schizophrenia module has very low sensitivity (20%) for measuring symptom duration (DSM-IV criteria C for SZ) when compared against diagnostic ratings made by experienced clinicians (136). It is possible that some participants with SZ were detected in the current research, and some of these false negatives may have been incorrectly classified as meeting criteria for MAP (in study five). Thus, this research could be improved with the use of strongly validated diagnostic tools, such as the Psychiatric Research Interview for DSM-IV Substance and Mental disorders (PRISM)(163).

Part F: Future research

The current research suggests that clinically significant primary negative symptoms may be less likely among those with methamphetamine-related psychoses relative to people with primary psychotic disorders (such as SZ). Further replication is needed to verify the association between polysubstance use (particularly heroin and benzodiazepines) and the frequency and severity of negative symptoms among people formally diagnosed with MAP, relative to a matched sample of people diagnosed with SZ. It would be informative for future research to test whether an absence of primary negative symptoms in MAP, but not SZ,

corresponds to differences in neural pathways, genetic variations, and neurocognitive impairments between these conditions.

Data-driven analyses could build upon the current research by examining whether syndromes of methamphetamine users can be derived based on other clinical features, beyond psychiatric symptoms (18, 70, 155). Kendler and colleagues (156) identified six latent classes of psychiatric patients based on measures of clinical signs (e.g. reduction in weight/appetite), course (e.g. benign versus chronic course), and outcome (e.g. poor versus good outcome), in addition to specific psychiatric symptoms. Among people who use methamphetamine, distinct latent syndromes might be characterised by differences in symptom duration (i.e. persistent versus transient), the number of prior episodes, mode of illness onset (i.e. gradual versus rapid onset), responsiveness to different treatments, social and occupational functioning, cognitive impairment, and genetic and family history factors. By including these clinical features, future latent class analyses would likely generate more precise and clinically useful demarcations between empirically-derived psychotic syndromes, and may provide insight into potential aetiological differences between the syndromes.

Exploring the nature and prevalence of cognitive impairment among methamphetamine users may be a promising avenue for differentiating forms of MAP from SZ. A growing body of evidence has recognised cognitive abnormalities as highly prevalent, albeit to varying degrees, among people with schizophrenia (70). These cognitive abnormalities appear to be generalised in nature and can have a profound impact on ones' functional outcome (183, 184). Likewise, heavy or long-term methamphetamine use may result in cognitive deficits that can persist despite abstinence from methamphetamine use. A recent review by Wearne and colleagues (164) found that cognitive domains appear to be similarly impaired across people with MAP and schizophrenia, and the authors suggested that

these similarities were “specifically comparable” for those with persistent or chronic MAP (164).

Future latent class analyses could guide attempts to refine the diagnostic criteria for MAP. The diagnostic instability associated with MAP (133-135) suggests that these criteria may not reliably exclude methamphetamine users who have other psychiatric conditions associated with delusional thinking or hallucinatory experiences (i.e. bipolar disorder, schizoaffective disorder, post-traumatic stress disorder, depressive psychosis, obsessive compulsive disorder, acute intoxication/withdrawal from methamphetamine, cannabis, alcohol, or other drugs (69, 157-162)). To clarify the diagnostic boundaries between MAP and these other psychiatric conditions, it would be informative to investigate whether these clinical groupings (MAP and other psychiatric disorder) correspond to different latent symptom profiles among people who use methamphetamine. In the current research (study five), symptoms of activation, tension, and conceptual disorganisation differentiated those with the high-pathology profile (associated with a diagnosis of SZ) from those with the moderate-pathology profile (associated with a diagnosis of MAP). Likewise, the findings of future latent class analyses may highlight novel symptoms, signs, and clinical indicators that differentiate MAP from other conditions. If applied to longitudinal data, data-driven techniques (such as latent growth curve modelling) could be useful in identifying whether certain syndromes are associated with a greater risk of transitioning from MAP to SZ later in life. This could identify clinical characteristics that more indicative of drug-precipitated SZ rather than a drug-induced psychosis.

It would be informative for future research to directly test whether MAP and SZ are represented by different underlying factors of psychiatric symptoms. This would be achieved by recruiting a large sample of people diagnosed with SZ and people diagnosed with MAP, who are matched on important covariates (such as history of substance use). These two

clinical groups should complete the same psychiatric symptom scale. The researchers could apply exploratory factor analysis to the data of people with MAP to identify the underlying factor structure of the disorder (in terms of the number of factors, and the items comprising those factors). Confirmatory factor analysis could then be applied to the data of people with SZ to test whether the factor structure underlying MAP also applies to SZ. If these disorders have a consistent factor structure of psychiatric symptoms, goodness of fit indices would indicate that the MAP factor structure model also accounts for the observed covariance among people with SZ.

A notable minority of people with MAP (25%) experience symptoms that persist beyond one month after intoxication. Further research is needed to document the prevalence and predictors of persistent MAP, and to understand the boundaries between persistent MAP, transient MAP, and SZ (164, 165). As highlighted in the systematic review (study one), very few researchers have examined the duration of psychotic symptoms among community samples of people who use methamphetamine, most likely due to difficulties in verifying periods of abstinence from methamphetamine. As a result, the extent of persistent MAP among the broader (non-institutionalised) community is unknown. Moreover, it is unclear how or why transient MAP develops into a more enduring illness for some people, and further longitudinal research is needed to examine the clinical correlates associated with a shift from transient to persistent MAP. As people with longer lasting episodes tend to have more severe psychotic symptoms (110), it would be informative to examine whether symptom severity predicts longer symptom duration, and whether this, in turn, is related to a diagnosis of SZ. Finally, people with SZ demonstrate irregularities in brain structure, physiology, and neurochemistry relative to the general population (48)), and it would informative to test whether these irregularities also exist in people with persistent MAP. Evidence reviewed by Wearne and colleagues (164) suggests that people with chronic (but

not transient) MAP display similar cognitive dysfunctions to people with SZ, implying that these two populations could share overlapping irregularities in brain function. If such characteristics are identified in persistent (but not transient) MAP, this would suggest that persistent MAP is qualitatively distinct from transient MAP, and may be reflect a precipitation of SZ.

Summary

Through the novel application of data-driven statistical techniques, this thesis provides a greater insight into the profile and underlying structure of psychotic symptoms associated with methamphetamine use. This symptom profile was examined among people recruited from the Australian community (rather than from in-patient settings), who constitute an underrepresented population within the methamphetamine-associated psychosis (MAP) literature. Prominent symptoms of MAP included persecutory delusions, auditory and visual hallucinations, and affective symptoms, and one-quarter of people with MAP experienced "persistent" psychotic symptoms that continue beyond one-month after drug cessation. A minority of people who use methamphetamine experienced negative symptoms; however, these symptoms were associated with polysubstance use (not methamphetamine use) and manifested among a different latent class of people who reported delusions and hallucinations. Thus, negative symptoms do not appear to be a component of MAP, and could be a point of differentiation from SZ. Two distinct psychotic syndromes were identified among people who use methamphetamine, which partially aligned with current diagnostic constructs. This is consistent with the notion that MAP is clinically distinct from SZ, and supports the practical utility of having a diagnostic construct of MAP to allow clinicians to draw inferences about psychosis liability and for guiding symptom management. A notable proportion of people who experienced psychotic symptoms were not captured in

the diagnostic groupings of MAP or SZ. This research demonstrates that greater consideration of specific symptoms (e.g., negative symptoms and non-persecutory delusions) may improve diagnostic accuracy by identifying people with a higher risk of SZ.

References

1. United Nations. (1971). *Convention on psychotropic substances*. Vienna, Austria: UN General Assembly.
2. Cruickshank, C., & Dyer, K. (2009). A review of the clinical pharmacology of methamphetamine. *Addiction, 104*(7): 1085-99.
3. Vearrier, D., Greenberg, M., Miller, S., Okaneku, J., & Haggerty, D. (2012). Methamphetamine: History, pathophysiology, adverse health effects, current trends, and hazards associated with the clandestine manufacture of methamphetamine. *Dis Mon, 58*(2):38-89.
4. Courtney, K., & Ray, L. (2014). Methamphetamine: An update on epidemiology, pharmacology, clinical phenomenology, and treatment literature. *Drug & Alcohol Dependence, 143*:11-21.
5. Australian Institute of Health and Welfare. (2017). *Drug Strategy Household Survey 2016: detailed findings*. Canberra, Australia: Australian Institute of Health and Welfare.
6. McKetin, R., Kaye, S., Clemens, K., & Hermens, D. (2013). Methamphetamine addiction. In: Diego S, editor. *Principles of addiction: Comprehensive addictive behaviors and disorders* (p. 689–98). San Diego: Academic Press.
7. Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug & Alcohol Review, 27*:253 – 62.
8. Kelly, P., Robinson, L., Baker, A., Deane, F., McKetin, R., Hudson, S., & Keane, C. (2017). Polysubstance use in treatment seekers who inject amphetamine: Drug use profiles, injecting practices and quality of life. *Addict Behav, 71*:25-30.
9. Anglin, M., Burke, C., Perrochet, B., Stamper, E., & Dawud-Noursi, S. (2000). History of the methamphetamine problem. *Journal of Psychoactive Drugs, 32*(2):137-41.
10. Grinspoon, L., & Hedblom, P. (1975). *The speed culture: Amphetamine use and abuse in America*. Cambridge, MA: Harvard University Press.
11. Rasmussen, N. (2009). *On speed: From Benzedrine to Adderall* (1st edition). New York: NYU Press;
12. Johnson, J., Milner, G.,& Marks, V. (1965). Diagnosis of amphetamine addiction. *The British Medical Journal, 1*(5431).

13. Wilens, T., Adler, L., Adams, J., Sgambati, S., Rotrosen, J., Sawtelle, R., & Utzinger, L., & Fusillo, S. (2008). Misuse and diversion of stimulants prescribed for ADHD: a systematic review of the literature. *J Am Acad Child Adolesc Psychiatry*, *47*(1): 21-31.
14. United Nations Office on Drugs and Crime. (2019). *World drug report 2019*. New York: United Nations Office on Drugs and Crime.
15. Degenhardt, L., Roxburgh, A., Black, E., Bruno, R., Campbell, G., Kinner, S., & Fetherston, J. (2008). The epidemiology of methamphetamine use and harm in Australia. *Drug and Alcohol Review, 27*(3):243-52.
16. McKetin, R., Hickey, K., Devlin, K., & Lawrence, K. (2010). The risk of psychotic symptoms associated with recreational methamphetamine use. *Drug Alcohol Rev, 9*(4):358-63.
17. McKetin, R., Kelly, E., & McLaren, J. (2006). The relationship between crystalline methamphetamine use and methamphetamine dependence. *Drug and Alcohol Dependence, 85*:198–204.
18. American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th edition). Arlington, VA: American Psychiatric Publishing.
19. Zorick, T., Nestor, L., Miotto, K., Sugar, C., Hellemann, G., Scanlon, G., Rawson, R., & London, E. (2010). Withdrawal symptoms in abstinent methamphetamine-dependent subjects. *Addiction, 105*(10):1809-18.
20. Degenhardt L, Larney S, Chan G, Dobbins T, Weier M, Roxburgh A, Hall, W., & McKetin, R. (2016). Estimating the number of regular and dependent methamphetamine users in Australia, 2002–2014. *The Medical Journal of Australia, 204*(4):153-9.
21. Hall, W., & Hando, J. (1994). Route of administration and adverse effects of amphetamine use among young adults in Sydney, Australia. *Drug and Alcohol Review, 13*(3); 277-284.
22. Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug & Alcohol Review, 27*:253 – 62.
23. Darke, S., & Hall, W. (1995). Levels and correlates of polydrug use among heroin users and regular amphetamine users. *Drug & Alcohol Dependence, 39*:231-5.
24. Brecht, M., Huang, D., Evans, E., & Hser, Y. (2008). Polydrug use and implications for longitudinal research: Ten-year trajectories for heroin, cocaine, and methamphetamine users. *Drug Alcohol Depend, 96*(3):193-201.
25. Mendelson, J., Jones, R., Upton, R., & Jacob, P. (1995). Methamphetamine and ethanol interactions in humans. *Clin Pharmacol Ther, 57*:559 – 68.

26. Grant, K., LeVan, T., Wells, S., Li, M., Stoltenberg, S., Gendelman, H., Carlo, G., & Bevins, R. (2012). Methamphetamine-associated psychosis. *Journal Of Neuroimmune Pharmacology, 7*(1):113-39.
27. Lecomte, T., Dumais, A., Dugré, J., & Potvin, S. (2018). The prevalence of substance-induced psychotic disorder in methamphetamine misusers: A meta-analysis. *Psychiatry Research, 268*:189-92.
28. Fasihpour, B., Molavi, S., & Shariat, S. (2013). Clinical features of inpatients with methamphetamine-induced psychosis. *J Ment Health, 22*(4):341-9.
29. Young, D., & Scoville,W. (1938). Paranoid psychosis in narcolepsy and the possible danger of benzedrine treatment. *Med Clin North Am, 22*:637–46.
30. Wallis, G., McHarg, J., & Scott, O. (1949). Acute psychosis caused by dextro-amphetamine. *Br Med J, 2*(4641):1394.
31. O'Flanagan, P., & Taylor, R. (1950). A case of recurrent psychosis associated with amphetamine addiction. *J Ment Sci, 96*(405):1033-6.
32. Herman, M., & Nagler, S. (1954). Psychoses due to amphetamine. *J Nerv Ment Dis, 120*(3-4):268-72.
33. Beamish, P., & Kiloh, L. (1960). Psychoses due to amphetamine consumption. *J Ment Sci, 106*:337-43.
34. Connell, P. (1958). *Amphetamine psychosis, Maudsley monograph no. 5*. London, UK: Oxford University Press.
35. Schulz, S., Schulz, P., Dommisse, C., Hamer, R., Blackard, W., Narasimhachari, N., & Friedel, R. (1985). Amphetamine response in borderline patients. *Psychiatry Res, 15*(2):97-108.
36. Griffith, J., Cavanaugh, J., Held, J., & Oates, J. (1972). Dextroamphetamine: Evaluation of psychomimetic properties in man. *Archives of General Psychiatry, 2*6(2):97-100.
37. Angrist, B., & Gershon, S. (1970). The phenomenology of experimentally induced amphetamine psychosis--preliminary observations. *Biological Psychiatry, 2*(2):95-107.
38. Chen, C., Lin, S., Sham, P., Ball, D., Loh, E., Hsiao, C., Chiang, Y., Ree, S., Lee, C., Murray, R. (2003). Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychological Medicine, 33*(8):1407-14.
39. Iwanami, A., Sugiyama, A., Kuroki, N., Toda, S., Kato, N., Nakatani, Y., Horita, N., & Kaneko, T. (1994). Patients with methamphetamine psychosis admitted to a psychiatric hospital in Japan: A preliminary report. *Acta Psychiatrica Scandinavica, 89*(6), 428-432.

40. McKetin, R., Dawe, S., Burns, R., Hides, L., Kavanagh, D., Teesson, M., Young, M., & Voce, A. (2016). The profile of psychiatric symptoms exacerbated by methamphetamine use. *Drug Alcohol Depend, 1*(161):104-9.
41. Szuster, R. (1990). Methamphetamine in psychiatric emergencies. *Hawaii Med J, 49*(10):389-91.
42. Akiyama, K., Saito, A., & Shimoda, K. (2011). Chronic methamphetamine psychosis after long-term abstinence in Japanese incarcerated patients. *American Journal on Addictions, 20*(3):240-9.
43. Hall, R., Popkin, M., Beresford, T., & Hall, A. (1988). Amphetamine psychosis: clinical presentations and differential diagnosis. *Psychiatr Med, 6*(1):73-9.
44. Srisurapanont, M., Ali, R., Marsden, J., Sunga, A., Wada, K., & Monteiro, M. (2003). Psychotic symptoms in methamphetamine psychotic in-patients. *Int J Neuropsychopharmacol, 6*(4):347-52.
45. Srisurapanont, M., Arunpongpaisal, S., Wada, K., Marsden, J., Ali, R., & Kongsakon, R. (2011). Comparisons of methamphetamine psychotic and schizophrenic symptoms: a differential item functioning analysis. *Progress in Neuro-Psychopharmacology & Biological Psychiatry, 35*(4):959-64**.**
46. Harris, D., & Batki, S. (2000). Stimulant psychosis: symptom profile and acute clinical course. *American Journal on Addictions, 9*(1):28-37.
47. Ali, R., Marsden, J., Srisurapanont, M., Sunga, A., Baigent, M., & Monteiro, M. (2010). Methamphetamine psychosis in Australia, Philippines, and Thailand: Recommendations for acute care and clinical inpatient management. *Addictive Disorders & Their Treatment, 9*(4): 143-149.
48. Castle, D., & Buckley. (2015). *Schizophrenia* (2nd edition). Oxford, United Kingdom: Oxford University Press.
49. Tomiyama, G. (1990). Chronic schizophrenia-like states in methamphetamine psychosis. *Japanese Journal of Psychiatry & Neurology, 44*(3):531-9.
50. Sato, M. (1992). A lasting vulnerability to psychosis in patients with previous methamphetamine psychosis. *Ann N Y Acad Sci, 654*:160-70.
51. Sato, M. (1986). Acute exacerbation of methamphetamine psychosis and lasting dopaminergic supersensitivity--a clinical survey. *Psychopharmacology Bulletin, 22*(3):751-6.

52. Sato, M., Chen, C., Akiyama, K., & Otsuki, S. (1983). Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biological Psychiatry, 18*(4); 429-440.
53. Sato, M., Numachi, Y., & Hamamura, T. (1992). Relapse of paranoid psychotic state in methamphetamine model of schizophrenia. *Schizophr Bull, 18*(1):115-22.
54. Akiyama, K. (2006). Longitudinal clinical course following pharmacological treatment of methamphetamine psychosis which persists after long-term abstinence. *Ann N Y Acad Sci, 1074*:125-34.
55. Yui, K., Goto, K., Ikemoto, S., & Ishiguro, T. (1995). Spontaneous recurrence of methamphetamine psychosis: process and monoamine neurotransmitter function. *Nihon Shinkei Seishin Yakurigaku Zasshi, 15*(4):363-74.
56. Yui, K., Ishiguro, T., Goto, K., & Ikemoto, S. (2000). Susceptibility to subsequent episodes in spontaneous recurrence of methamphetamine psychosis. *Ann N Y Acad Sci, 914*:292-302.
57. Yui, K., Goto, K., Ikemoto, S., & Ishiguro, T. (2000). Stress induced spontaneous recurrence of methamphetamine psychosis: The relation between stressful experiences and sensitivity to stress. *Drug and Alcohol Dependence, 58*(1-2), 67-75.
58. Yui, K., Goto, K., Ikemoto, S., Ishiguro, T., & Kamata, Y. (2000). Increased sensitivity to stress in spontaneous recurrence of methamphetamine psychosis: Noradrenergic hyperactivity with contribution from dopaminergic hyperactivity. *Journal of Clinical Psychopharmacology, 20*(2): 165-174.
59. Yui, K., Ikemoto, S., & Goto, K. (2002). Factors for susceptibility to episode recurrence in spontaneous recurrence of methamphetamine psychosis. *Annals of the New York Academy of Sciences, 965*:292-304.
60. Laruelle, M. (2000). The role of endogenous sensitization in the pathophysiology of schizophrenia: implications from recent brain imaging studies. *Brain Res Rev, 31*(2-3): 371-84.
61. Maia, T., & Frank, M. (2017). An integrative perspective on the role of dopamine in schizophrenia. *Biological Psychiatry, 81*:52-66.
62. World Health Organisation. (2018). *International statistical classification of diseases and related health problems* (11th revision). Geneva: World Health Organization.
63. McIver, C., McGregor, C., Baigent, M., Spain, D., Newcombe, D., & Ali, R. (2006). *Guidelines for the medical management of patients with methamphetamine induced psychosis*. South Australia: Drug and Alcohol Services South Australia.

64. Flaum, M., & Schultz, S. (1996). When does amphetamine-induced psychosis become schizophrenia? *Am J Psychiatry, 153*(6):812-5.
65. Mathias, S., Lubman, D., & Hides, L. (2008). Substance-induced psychosis: a diagnostic conundrum. *Journal of Clinical Psychiatry, 69*(3):358-67.
66. Leucht, S., Cipriani, A., Spineli, L., Mavridis, D., Orey, D., Richter, F., Samara, M., Barbui, C., Engel, R., Geddes, J., Kissling, W., Stapf, M., Lässig, B., Salanti, G., & Davis, J. (2013). Comparative Efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *Lancet, 382*(9896):951-62.
67. Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry, 62*(9):975-83.
68. Sara, G., Large, M., Matheson, S., Burgess, P., Malhi, G., Whiteford, H., & Hall, W. (2015). Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation. *Aust N Z J Psychiatry, 49*(2):106-17.
69. Hides, L., Dawe, S., McKetin, R., Kavanagh, D., Young, R., Teesson, M., Saunders, J. (2015). Primary and substance-induced psychotic disorders in methamphetamine users. *Psychiatry Research, 226*(1):91-6.
70. Tandon, R., Keshavan, M., & Nasrallah, H. (2008). Schizophrenia, “Just the Facts” What we know in 2008: Epidemiology and etiology. *Schizophrenia Research, 102*:1–18.
71. Callaghan, R., Cunningham, J., Allebeck, P., Arenovich, T., Sajeev, G., Remington, G., Boileau, I., & Kish, S. (2012). Methamphetamine use and schizophrenia: a population-based cohort study in California. *Am J Psychiatry, 169*(4):389-96.
72. Curran, C., Byrappa, N., & McBride, A. (2004). Stimulant psychosis: systematic review. *Br J Psychiatry, 185*:196-20.
73. Drake, R., Caton, C., Xie, H., Hsu, E., Gorroochurn, P., Samet, S., & Hasin, D. (2011). A prospective 2-year study of emergency department patients with early-phase primary psychosis or substance-induced psychosis. *American Journal of Psychiatry, 168*(7):742-8.
74. Sweeting, M., & Farrell, M. (2005). Metamphetamine psychosis: How is it related to schizophrenia? A review of the literature. *Current Psychiatry Reviews, 1*(2); 115-122.
75. Fraser, S., Hides, L., Philips, L., Proctor, D., & Lubman, D. (2012). Differentiating first episode substance induced and primary psychotic disorders with concurrent substance use in young people. *Schizophrenia Research, 136*(1-3):110-5.
76. Bell, D. (1965). Comparison of amphetamine psychosis and schizophrenia. *Br J Psychiatry, 111*:701-7.

77. Zeidman, H., Oscherwitz, M., & Addario, D. (1975). Amphetamine psychosis or paranoid schizophrenia? *West J Med, 122*(5):394-405.
78. Zarrabi, H., Khalkhali, M., Hamidi, A., Ahmadi, R., & Zavarmousavi, M. (2016). Clinical features, course and treatment of methamphetamine-induced psychosis in psychiatric inpatients. *BMC Psychiatry, 16*(44).
79. Medhus, S., Mordal, J., Holm, B., Mørland, J., & Bramness, J. (2013). A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. *Psychiatry Research, 206*(1):17-21.
80. Patel, R., Jayatilleke, N., Broadbent, M., Chang, C., Foskett, N., Gorrell, G., Hayes, R., Jackson, R., Johnston, C., Shetty, H., Roberts, A., McGuire, P., & Stewart, R. (2015). Negative symptoms in schizophrenia: a study in a large clinical sample of patients using a novel automated method. *BMJ Open, 5*(9).
81. Chen, C., Lin, S., Chen, Y., Huang, M., Chen, T., Ree, S., & Wang, L. (2015). Persistence of psychotic symptoms as an indicator of cognitive impairment in methamphetamine users. *Drug and Alcohol Dependence, 148*: 158-164.
82. Panenka, W., Procyshyn, R., Lecomte, T., MacEwan, W., Flynn, S., Honer, W., Barr, A. (2012). Methamphetamine use: A comprehensive review of molecular, preclinical and clinical findings. *Drug and Alcohol Dependence, 129*(3):167-79.
83. Bramness, J., Gundersen, O., Guterstam, J., Rognli, E., Konstenius, M., Loberg, E., Medhus, S., Tanum, L., & Franck, J. (2012). Amphetamine-induced psychosis--a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry, 12*:221.
84. Chen, C., Lin, S., Sham, P., Ball, D., Loh, W., Murray, R. (2005). Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *Am J Med Genet B Neuropsychiatr Genet, 136B*(1):87-91.
85. Miettunen, J., Nordström, T., Kaakinen, M., & Ahmed, A. (2016). Latent variable mixture modeling in psychiatric research - a review and application. *Psychological Medicine, 46*(3): 457-67.
86. Bollen, K. (2002). Latent variables in psychology and the social sciences. *Annual Review of Psychology, 53*:605-34.
87. Bousman, C., McKetin, R., Burns, R., Woods, S., Morgan, E., Atkinson, J., Everall, I., Grant, I., TMARC Group. (2015). Typologies of positive psychotic symptoms in methamphetamine dependence. *American Journal on Addictions, 24*(2):94-7.

88. Vehkalahti, K. (2010). Foundations of factor analysis (2nd edition). *International statistical review, 78*(2):327-8.
89. Bartholomew, D., Knott, M., & Moustaki, I. (2013). *Latent variable models and factor analysis: A unified approach* (3rd edition). United States: Wiley.
90. Fabrigar, L., Wegener, D., MacCallum, R., & Strhan, E. (1999). Evaluating the use of exploratory factor analysis in psychological research. *Psychological Methods, 4*(3):272-99.
91. Yong, A., & Pearce, S. (2013). A beginner's guide to factor analysis: Focusing on exploratory factor analysis. *Tutorials in Quantitative Methods for Psychology, 9*(2):79-94.
92. Matsunaga, M. (2010). How to factor-analyze your data right: Do's, don'ts, and how-to's. *International Journal of Psychological Research, 3*(1):2011-84.
93. Abdi, H., & Williams, L. (2010). Principal component analysis. *Computational Statistics, 4*(2): 433-59.
94. Fanous, A., Gardner, C., Walsh, D., & Kendler, K. (2001). Relationship between positive and negative symptoms of schizophrenia and schizotypal symptoms in nonpsychotic relatives. *Arch Gen Psychiatry, 58*(7):669-73.
95. Cardno, A., Sham, P., Murray, R., & McGuffin, P. (2001). Twin study of symptom dimensions in psychoses. *Br J Psychiatry, 179*:39-45.
96. Guerra, A., Fearon, P., Sham, P., Jones, P., Lewis, S., Mata, I., & Murray, R. (2002). The relationship between predisposing factors, premorbid function and symptom dimensions in psychosis: an integrated approach. *Eur Psychiatry, 17*:311–20.
97. O'Leary, D., Flaum, M., Kesler, M., Flashman, L., Arndt, S., & Andreasen, N. (2000). Cognitive correlates of the negative, disorganized, and psychotic symptom dimensions of schizophrenia. *J Neuropsychiatry Clin Neurosci, 12*(1):4-15.
98. Norman, R., Malla, A., Morrison-Stewart, S., Helmes, E., Williamson, P., Thomas, J., & Cortese, L. (1997). Neuropsychological correlates of syndromes in schizophrenia. *British Journal of Psychiatry, 170*:134-9.
99. Rietkerk, T., Boks, M., Sommer, I., Liddle, P., Ophoff, R., & Kahn, R. (2008). The genetics of symptom dimensions of schizophrenia: review and meta-analysis. *Schizophrenia Research, 102*:197–205.
100. Muthén, B. (2004). Latent variable analysis: Growth mixture modeling and related techniques for longitudinal data. In: *Handbook of quantitative methodology for the social sciences*, by D. Kaplan (editor). Newbury Park, CA: Sage
101. Hagenaars, J., & McCutcheon, A. (2002). *Applied latent class analysis*. New York: Cambridge University Press.

102. Schafer, J. (1999). Multiple imputation: a primer. *Stat Methods Med Res, 8*(1):3-15.
103. Yang, C. (2006). Evaluating latent class analysis models in qualitative phenotype identification. *Comput Stat Data Anal, 50*(4):1090-104.
104. Rosen C, Grossman, L.S., Harrow, M., Bonner-Jackson, A., & Faull, R. (2011). Diagnostic and prognostic significance of Schneiderian first-rank symptoms: a 20-year longitudinal study of schizophrenia and bipolar disorder. *Compr Psychiatry, 5*2:126–31.
105. McKetin, R., McLaren, J., Lubman, D., & Hides, L. (2006). The prevalence of psychotic symptoms among methamphetamine users. *Addiction, 101*(10):1473-8.
106. Ellinwood, E. (1967). Amphetamine psychosis: Description of the individuals and process. *Journal of Nervous and Mental Disease, 144*(4): 273-283.
107. Jonsson, L., & Sjostrom, K. (1970). A rating scale for evaluation of the clinical course and symptomatology in amphetamine psychosis. *British Journal of Psychiatry, 117*(541):661-5.
108. Bramness, J., Gundersen, O., Guterstam, J., Rognli, E., Konstenius, M., Loberg, E., Medhus, S., Tanum, L., & Franck, J. (2012). Amphetamine-induced psychosis--a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry, 12*:221.
109. Bell, D. (1973). The experimental reproduction of amphetamine psychosis. *Archives of General Psychiatry, 29*(1): 35-40.
110. Lecomte, T., Mueser, K., MacEwan, W., Thornton, A., Buchanan, T., Bouchard, V., Goldner, E., Brink, J., Lang, D., Barr, A., & Honer, W. (2013). Predictors of persistent psychotic symptoms in persons with methamphetamine abuse receiving psychiatric treatment. *Journal of Nervous & Mental Disease, 201*(12):1085-1089.
111. Aguilar de Arcos, F., Verdejo-García, A., Ceverino, A., Montañez-Pareja, M., López-Juárez, E., Sánchez-Barrera, M., López-Jiménez, A., Pérez-García, M., & PEPSA team. (2008). Dysregulation of emotional response in current and abstinent heroin users: negative heightening and positive blunting. *Psychopharmacology, 198*(2):159-66.
112. Golan, D., Tashjian, A., Armstrong, E., & Armstrong, A. (2008). Principles of pharmacology: The pathophysiologic basis of drug therapy (2nd edition). Baltimore: LWW Publishers.
113. Savvas, S., Somogyi, A, & White, J. (2012). The effect of methadone on emotional reactivity. *Addiction, 107*(2):388-92.
114. Miller, M., Bershad, A., & de Wit, H. (2015). Drug effects on responses to emotional facial expressions: recent findings. *Behav Pharmacol, 26*(6):571-9.

115. Sanfilipo, M., Wolkin, A., Angrist, B., van Kammen, D., Duncan, E., Wieland, S. (1996). Amphetamine and negative symptoms of schizophrenia: *Psychopharmacology, 123*(2): 211-214.
116. Willi, T., Honer, W., Thornton, A., Gicas, K., Procyshyn, R., Vila-Rodriguez, F., Panenka, W., Aleksic, A., Leonova, O., Jones, A., MacEwan, G., & Barr, A. (2016). Factors affecting severity of positive and negative symptoms of psychosis in a polysubstance using population with psychostimulant dependence. *Psychiatry Research, 240*(30):336-42.
117. Viktorin, A., Rydén, E., Thase, M., Chang, Z., Lundholm, C., D'onofrio, B., Almqvist, C., Magnusson, P., Lichtenstein, P., Larsson, H., Landén, M. (2017). The risk of treatment-emergent mania with methylphenidate in bipolar disorder. *Am J Psychiatr Clin, 174*:341-8.
118. Bramness, J., Gundersen, O., Guterstam, J., Rognli, E., Konstenius, M., Loberg, E., Medhus, S., Tanum, L., & Franck, J. (2012). Amphetamine-induced psychosis--a separate diagnostic entity or primary psychosis triggered in the vulnerable? *BMC Psychiatry, 12*:221.
119. Millan, M., Fone, K., Steckler, T., & Horan, W. (2014). Negative symptoms of schizophrenia: clinical characteristics, pathophysiological substrates, experimental models and prospects for improved treatment. *Eur Neuropsychopharmacol, 24*(5):645-92.
120. Havers, L., Taylor, M., & Ronald, A. (2019). Genetic and environmental influences on the stability of psychotic experiences and negative symptoms in adolescence. *J Child Psychol Psychiatry, 60*(7):784-92.
121. Shin, M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology, 35*(1):169-91.
122. Voce, A., Calabria, B., Burns, R., Castle, D., & McKetin, R. (2019). A systematic review of the symptom profile and course of methamphetamine associated psychosis. *Substance Use & Misuse, 54*(4):549-59.
123. Kendler, K., Ohlsson, H., Sundquist, J., & Sundquist, K. (2019). Prediction of onset of substance-induced psychotic disorder and Its progression to schizophrenia in a Swedish national sample. *Am J Psychiatry, 176*(9):711-9.
124. Berry, A., & Cirulli, F. (2016). Toward a diathesis-stress model of schizophrenia in a neurodevelopmental perspective. Handbook of Behavioral Neuroscience, 23(13):209-24.
125. Arunogiri, S., Foulds, J., McKetin, R., & Lubman, D. 2018. A systematic review of risk factors for methamphetamine-associated psychosis. *Australian & New Zealand Journal of Psychiatry, 52*(6): 514-52.
126. Kendell, R. (1989). Clinical validity. *Psychological Medicine, 19*:45-55.

127. Kendell, R. (1975). The concept of disease and its implications for psychiatry. *The British Journal of Psychiatry, 127*:305-15.
128. American Psychiatric Association. (2016). *Practice Guidelines for the Psychiatric Evaluation of Adults*, 3rd Edition. Arlington, VA: American Psychiatric Association.
129. Peralta, V., Cuesta, M., Giraldo, C., Cardenas, A., & Gonzalez, F. (2002). Classifying psychotic disorders: issues regarding categorial vs. dimensional approaches and time frame to assess symptoms. *Eur Arch Psychiatry Clin Neurosci, 252*:12-8.
130. Lage, D., Egli, S., Riedel, M., Strauss, A., & Moller, H. (2011). Combining the categorical and the dimensional perspective in a diagnostic map of psychotic disorders. *Eur Arch Psychiatry Clin Neurosci, 261*:3–10.
131. Potuzak, M., Ravichandran, C., Lewandowski, K., Ongür, D., & Cohen, B. (2012). Categorical vs dimensional classifications of psychotic disorders. *Compr Psychiatry, 53*(8):1118-29.
132. Peralta, V., & Cuesta, M. (2000). Clinical models of schizophrenia: a critical approach to competing conceptions. *Psychopathology, 33*:252–8.
133. Kittirattanapaiboon, P., Mahatnirunkul, S., Booncharoen, H., Thummawomg, P., Dumrongchai, U., & Chutha, W. (2010). Long-term outcomes in methamphetamine psychosis patients after first hospitalisation. *Drug Alcohol Rev, 29*(4):456-61.
134. Niemi-Pynttäri, J., Sund, R., Putkonen, H., Vorma, H., Wahlbeck, K., & Pirkola, S. (2013). Substance-induced psychoses converting into schizophrenia: A register-based study of 18,478 finnish inpatient cases. *Journal of Clinical Psychiatry, 74*(1):e94-e9.
135. Alderson, H., Semple, D., Blayney, C., Queirazza, F., Chekuri, V., & Lawrie, S. (2017). Risk of transition to schizophrenia following first admission with substance-induced psychotic disorder: a population-based longitudinal cohort study. *Psychol Med, 47*(14):2548-55.
136. Cooper, L., Peters, L., & Andrews, G. (1998). Validity of the composite international diagnostic interview (CIDI) psychosis module in a psychiatric setting. *Journal of Psychiatric Research, 32*:361-8.
137. McKetin, R., Kelly, E., & McLaren, J. (2005). The characteristics of treatment provided for amphetamine use in New South Wales, Australia. *Drug & Alcohol Review, 24*:433-6.
138. McKetin, R., Lubman, D., Najman, J., Dawe, S., Butterworth, P., & Baker, A. (2014). Does methamphetamine use increase violent behaviour? Evidence from a prospective longitudinal study. *Addiction, 109*(5):798-806.

139. McKetin, R., McLaren, J., Lubman, D., & Hides, L. (2008). Hostility among methamphetamine users experiencing psychotic symptoms. *Am J Addict, 17*(3):235-40.
140. Grigg, J., Arunogiri, S., Volpe, I., Frei, M., Phan, V., Rubenis, A., Dias, S., Petrie, M., Sharkey, M., & Lubman, D. (2018). *Methamphetamine treatment guidelines: Practice guidelines for health professionals* (2nd edition). Richmond, Victoria: Turning Point.
141. Ritsher, J., Lucksted, A., Otilingam, P., & Grajales, M. (2004). Hearing voices: Explanations and implications. *Psychiatric Rehabilitation Journal Winter, 27*(3):219-227.
142. Hoftman, G. (2017). The burden of mental illness beyond clinical symptoms: Impact of stigma on the onset and course of schizophrenia spectrum disorders. *Am J Psychiatry, 11*(4):5-7.
143. Hartley, S., Barrowclough, C., & Haddock, G. (2013). Anxiety and depression in psychosis: a systematic review of associations with positive psychotic symptoms. *Acta Psychiatr Scand, 128*:327-46.
144. Heese, M. (2004). Achieving abstinence by treating depression in the presence of substance-use disorders. *Addictive Behaviors, 29*(6):1137-41.
145. Falkenberg, I., Valmaggia, L., Byrnes, M., Frascarelli, M., Jones, C., Rocchetti, M., Straube, B., Badger, S., McGuire, P., & Fusar-Poli, P. (2015). Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? *Psychiatry Research, 228*(3):808-15.
146. Sara, G., Large, M., Matheson, S., Burgess, P., Malhi, G., Whiteford, H., & Hall, W. (2015). Stimulant use disorders in people with psychosis: a meta-analysis of rate and factors affecting variation. *Aust N Z J Psychiatry, 49*(2):106-17.
147. Cosoff, S., & Hafner, R. (1998). The prevalence of comorbid anxiety in schizophrenia, schizoaffective disorder and bipolar disorder. *Aust N Z J Psychiatry, 32*:67-72.
148. Lubman, D., King, J., & Castle, D. (2010). Treating comorbid substance use disorders in schizophrenia. *Int Rev Psychiatr, 22*:191-201.
149. Winklbaur, B., Ebner, N., Sachs, G., Thau, K., & Fischer, G. (2006). Substance abuse in patients with schizophrenia. *Dialogues in clinical neuroscience, 8*(1):37-43.
150. Degenhardt, L., & Hall, W. (2001). The association between psychosis and problematical drug use among Australian adults: Findings from the national survey of mental health and well-being. *Psychological Medicine, 31*(4):659-68.
151. Gregg, L., Barrowclough, C., & Haddock, G. (2007). Reasons for increased substance use in psychosis. *Clin Psychol Rev, 27*(4):494-510.

152. Sara, G., Burgess, P., Malhi, G., Whiteford, H., & Hall, W. (2013). Differences in associations between cannabis and stimulant disorders in first admission psychosis. *Schizophrenia Research, 147*(2-3):216-22.

153. Hall, W., & Degenhardt, L. (2008). Cannabis use and the risk of developing a psychotic disorder. *World Psychiatry, 7*(2):68-71.

154. Cuzen, N., Koopowitz, S., Ferrett, H., Stein, D., Yurgelun, T. (2015). Methamphetamine and cannabis abuse in adolescence: a quasi-experimental study on specific and long-term neurocognitive effects. *BMJ Open, 5*:e005833.

155. Derks, E., Allardyce, J., Boks, M., Vermunt, J., Hijman, R., & Ophoff, R. (2012). Kraepelin was right: A latent class analysis of symptom dimensions in patients and controls. *Schizophrenia Bulletin, 38*:495–505.

156. Kendler, K., Karkowski, L., & Walsh, D. (1998). The structure of psychosis: latent class analysis of probands from the Roscommon family study. *Arch Gen Psychiatry, 55*:492-9.

157. Akindipe, T., Wilson, D., & Stein, D. (2014). Psychiatric disorders in individuals with methamphetamine dependence: Prevalence and risk factors. *Metabolic Brain Disease, 29*(2), 351-357.

158. Bartu, A., Freeman, N., Gawthorne, G., Codde, J., & Holman, C. (2003). Psychiatric comorbidity in a cohort of heroin and amphetamine users in Perth, Western Australia. *J Subst Use, 8*(3):150-4.

159. Lecomte, T., Mueser, K., MacEwan, W., Laferriere-Simard, M., Thornton, A., Buchanan, T., Brink, J., Ehmann, T., Lang, D., Kang, S., Barr, A., & Honer, W. (2010). Profiles of individuals seeking psychiatric help for psychotic symptoms linked to methamphetamine abuse. *Ment Health Subst Use: Dual Diagn, 3*(3):168-81

160. Salo, R., Flower, K., Kielstein, A., Leamon, M., Nordahl, T., & Galloway G. (2011). Psychiatric comorbidity in methamphetamine dependence. *Psychiatry Research, 186*(2-3):356-61.

161. Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug and Alcohol Review, 27*:253–262.

162. Eslami-Shahrbabaki, M., Fekrat, A., & Mazhari, S. (2015). A study of the prevalence of psychiatric disorders in patients with methamphetamine-induced psychosis. *Addict Health, 7*(1-2): 37-46.

163. Hasin, D., Trautman, K., Miele, G., Samet, S., Smith, M., & Endicott, J. (1996). Psychiatric Research Interview for Substance and Mental Disorders (PRISM): reliability for substance abusers. *Am J Psychiatry, 153*(9): 1195-201.

164. Wearne, T., & Cornish, J. (2018). A comparison of methamphetamine-induced psychosis and schizophrenia: A review of positive, negative, and cognitive symptomatology. *Front Psychiatry, 9*:491.

165. McKetin, R., Baker, A., Dawe, S., Voce, A., & Lubman, D. (2017). Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Res, 251*:349-54.

166. American Psychiatric Association. (2000). *Diagnostic and statistical manual of mental disorders* (4th edition, text revision). Arlington, VA: American Psychiatric Publishing.

167. Kulhalli, V., Isaac, M., & Murthy, P. (2007). Cannabis-related psychosis: Presentation and effect of abstinence. *Indian Journal of Psychiatry, 49*(4), 256–261.

168. Jordaan, G., & Emsley, R. (2013). Alcohol-induced psychotic disorder: a review. *Metab Brain Dis*, 29(2):231-43.

169. Everitt, B. (1993). *Cluster Analysis*. London: Edward Arnold.

170. Fuente-Tomas, L., Arranz, B., Safont, G., Sierra, P., Sanchez-Autet, M., Garcia-Blanco, A., & Garcia-Portilla, M. (2019). Classification of patients with bipolar disorder using k-means clustering. *PloS one, 14*(1), e0210314.

171. Sheaves, B., Porcheret, K., Tsanas, A., Espie, C. A., Foster, R. G., Freeman, D., Harrison, P. J., Wulff, K., & Goodwin, G. M. (2016). Insomnia, nightmares, and chronotype as markers of risk for severe mental illness: Results from a student population. *Sleep, 39*(1), 173–181.

172. Magidson, J., & Vermunt, J. (2002). Latent class models for clustering: A comparison with K-means. *Canadian Journal of Marketing Research, 20*: 37–44.

173. Schwartz, G. (1978). Estimating the dimension of a model. *The Annals of Statistics, 6*, 461–464.

174. Castle, D. J., Sham, P. C., Wessely, S., & Murray, R. M. (1994). The subtyping of schizophrenia in men and women: A latent class analysis. *Psychological Medicine, 24*(1), 41–51.

175. Burns J. K. (2013). Pathways from cannabis to psychosis: a review of the evidence. *Frontiers in Psychiatry, 4*, 128.

176. Picardi, A., Viroli, C., Tarsitani, L., Miglio, R., de Girolamo, G., Dell'Acqua, G., & Biondi, M. (2012). Heterogeneity and symptom structure of schizophrenia. *Psychiatry Research, 198*(3):386-94.

177. Feczko, E., Miranda-Dominguez, O., Marr, M., Graham, A. M., Nigg, J. T., & Fair, D. A. (2019). The heterogeneity problem: Approaches to identify psychiatric subtypes. *Trends in Cognitive Sciences, 23*(7), 584–601.

178. Jablensky A. (2010). The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues in Clinical Neuroscience, 12*(3), 271–287.

179. Ashok, A., Marques, T., Jauhar, S., Nour, M., Goodwin, G., Young, A., & Howes, O. (2017). The dopamine hypothesis of bipolar affective disorder: the state of the art and implications for treatment. *Molecular Psychiatry*, *22*(5), 666–679.

180. McIntyre, R., Berk, M., Brietzke, E., Goldstein, B., López-Jaramillo, C., et al. (2020). Bipolar disorders. *Lancet, 396*: 1841–56.

181. Cloninger, C. (1999). A new conceptual paradigm from genetics and psychobiology for the science of mental health. *Aust N Z J Psychiatry, 33*:174-186.

182. Kendler K. S. (2016). The nature of psychiatric disorders. *World Psychiatry, 15*(1), 5–12.

183. Bowie, C., Leung, W., Reichenberg, A., McClure, M., Patterson, T., Heaton, R., & Harvey, P. (2008). Predicting schizophrenia patients' real world behavior with specific neuropsychological and functional capacity measures. *Biol. Psychiatry 63*, 505–511.

184. Dickinson, D., Ragland, J., Gold, J., & Gur, R. (2008). General and specific cognitive deficits in schizophrenia: Goliath defeats David. *Biol. Psychiatry, 64*, 823–827.

Appendix A:

Rejoinder to Thesis Examiners' Comments

The following rejoinder provides responses to specific comments made by the thesis examiners. Comments are summarised (rather than provided verbatim) to protect confidentiality.

Response One

Examiner one raised the comment that the association between methamphetamine use and depressive symptoms (dysphoria and anhedonia) in study two may be interpreted through the dopamine hypothesis of depression. In study two, those with schizophrenia who had used amphetamine during the past-year were 1.9 times more likely to report anhedonia than those who had not. It is possible that these depressive symptoms were related to methamphetamine-related dopamine depletion over time. Methamphetamine intoxication increases synaptic concentrations of dopamine, which is associated with elevations in mood (Hellem et al., 2015), which are then depleted during withdrawal from the drug. Chronic methamphetamine use may lead to long-term disruption in dopamine responsivity (Jan et al., 2012; Nordahl et al., 2003). There is compelling evidence that downregulation of the dopamine system is involved in anhedonia – a diminished interest or pleasure in stimuli that one previously found rewarding – which is a core symptom of depression (Belujon & Grace, 2017). Thus, chronic methamphetamine use is hypothesised to predispose some people to develop depression. Depression is well-documented among chronic methamphetamine users (Darke et al., 2008), with some estimating that 40 percent of people entering treatment for methamphetamine use meet criteria for a major depressive episode in the previous year (McKetin et al., 2011). In study three, we identified a discrete affective symptom factor (i.e depression, anxiety, suicidality) that was positively correlated with frequency of methamphetamine use and severity of methamphetamine dependence. The affective symptoms factor shared a moderate positive correlation with the positive symptoms factor; consistent with the notion that a common mechanism (e.g. dopamine dysfunction) associated with methamphetamine use may contribute to both symptom factors.

Response Two

Examiner two raised the question about whether severity of symptoms may differentiate people with MAP and SZ. Using data for study five, I compared those who met criteria for MAP against those who met criteria for SZ on their severity of persecutory delusions and hallucinations (as the most common positive psychotic symptoms across both groups). The mean severity of persecutory delusions was higher among those who met criteria for SZ (M = 4.1; SD = 2.2) relative to those who met criteria for MAP (M = 2.7; SD = 1.4; t = -3.33, p=.0012). Similarly, the mean severity of hallucinations was higher among those who met criteria for SZ (M = 4.7; SD = 1.7) relative to those who met criteria for MAP (M = 2.6; SD = 1.3; t = -5.96, p=<.0001). This contrasts with Medhus and colleagues (2013), who demonstrated that patients with methamphetamine-related psychoses exhibited hallucinations, delusions, and suspiciousness at the same rate of severity and prevalence as patients with SZ who screened negative for methamphetamines. It would be informative for future research to examine whether methamphetamine users who meet criteria for SZ tend to cluster into different latent classes than those who meet criteria for MAP based on their severity (rather than prevalence) of psychiatric symptoms. This research question should be examined in both community and clinical populations.

Response Three

Examiner two raised the issue of diagnosis for people who continue to use methamphetamine and experience enduring psychotic symptoms (e.g. between 1 – 6 months). This common clinical challenge is well-described in the literature (Bell 1973; Fraser, et al., 2012; Mathias et al., 2008; Zeidman et al., 1975). Distinguishing between schizophrenia (SZ) and methamphetamine-associated psychoses (MAP) often relies on the degree to which methamphetamine can be implicated in the maintenance of psychosis, for which an adequate

period of abstinence from methamphetamine and other substances is vital but often very difficult to attain (McIver et al., 2006). Accurate diagnoses can often only be made in retrospect weeks or months after initial assessment, by which stage, clinicians necessarily have already implemented a course of treatment. When tracking the outcomes of 135 patients with stimulant dependence and chronic psychosis, Shaner and colleagues (1998) reported that a definitive diagnosis could not be made in more than 80% of cases, primarily due to insufficient periods of abstinence. Based on our current knowledge and diagnostic tools, it is not possible to assess the role of methamphetamine use in the aetiology or maintenance of psychosis without obtaining a clear window of abstinence (Sweeting & Farrell, 2005). In cases of persistent psychosis associated with methamphetamine use, clinicians should aim to minimise any exacerbating factors that may contribute to psychotic vulnerability.

Response Four

Examiner two raised the question of whether MAP is attributable to methamphetamine exposure, a predisposition to psychosis, or both. If MAP resulted soley from exposure to methamphetamine, this hypothesis would predict that there would be no difference in measures of psychosis vulnerability between people with and without MAP. This conflicts with findings by Chen and colleagues (2005), who reported that methamphetamine users with a history of MAP are five-times more likely to have a family member with SZ relative to users without a history of MAP. Likewise, Kendler and colleagues (2019) reported that those with stimulant-induced psychosis had significantly elevated familial risk scores for psychosis compared to stimulant users who did not have stimulant-induced psychosis. This suggests that an individual's predisposition to psychosis plays an important role in the emergence of MAP. However, another key finding of Kendler and colleagues (2019) was that the average familial risk of psychosis varied across different

types of substance-induced psychosis, ranging from alcohol (lowest) to cannabis (highest), with methamphetamine in between. Thus, the particular pharmacologic effects of methamphetamine also contribute to the emergence of MAP. The finding that MAP is likely attributable to a combination of both exposure to methamphetamine and an individuals' psychotic vulnerability conflicts with the notion that virtually all individuals (regardless of their vulnerability to psychosis) could develop schizophrenia with sufficient exposure to methamphetamine. Indeed, some people do not develop psychotic symptoms despite years of chronic methamphetamine use (Glasner-Edwards & Mooney, 2014), or despite being administered exceedingly high doses of amphetamines consistently over several days in experimental settings (Angrist & Gershon, 1970; McKetin, 2018). This body of evidence also suggests that not all forms of methamphetamine-related psychoses are a precipitation of SZ. Kendler and colleagues (2019) found that people with MAP who transitioned to a diagnosis of SZ had the same elevated familial risk for psychosis as people with an initial diagnosis of SZ, concluding that SZ following MAP is better explained as a drug-precipitated disorder in vulnerable individuals rather than a drug-induced syndrome.

Examiner two further raised an issue regarding the possible role of methamphetamine neurotoxicity in precipitating schizophrenia. Indeed, there is evidence that methamphetamine (like other drugs of abuse) may precipitate schizophrenia among people vulnerable to the disorder. Whilst psychosis liability is associated with a diagnosis of schizophrenia among people who use methamphetamine (Kendler et al., 2019), the effects of long-term methamphetamine use may also increase vulnerability to schizophrenia by causing long-lasting, or permanent, changes in brain structure or function that are associated with the disorder (Flaum & Schultz, 1996; Grant, et al., 2012). Chronic methamphetamine use has been shown to lead to long-term neurotoxic changes in brain structure, physiology, and chemistry (Jan et al., 2012; Yu et al., 2015). Methamphetamine use disrupts monoamine

function (i.e. dopamine, serotonin and glutamate systems), which in turn likely contributes to the widespread psychiatric disturbances observed in chronic methamphetamine users (Chang et al., 2007; Nordahl et al., 2003). In particular, chronic or heavy methamphetamine use is associated with dopaminergic dysfunction, which according to the dopamine hypothesis, underlie psychotic symptoms among people with schizophrenia (Maia & Frank, 2017). Thus, among people with a predisposition to schizophrenia (e.g. family history), neurotoxicity caused by long-term exposure to methamphetamine may be a key factor in precipitating the onset of a schizophrenic disorder.

Response Five

Examiner two requested further detail on the role of traumatic experiences as a key confounding factor that may precipitate both psychosis and substance use among people who use methamphetamine. Early trauma is a recognised environmental risk factor for the development of psychotic disorders, and the likelihood of experiencing psychosis is more than five-times higher for people who have experienced childhood trauma relative to those who have not (Barrigón et al., 2015; Harley et al., 2010). Although the mechanism underlying this relationship is unknown, it is hypothesised that trauma may prompt neurobiological and cognitive changes that predispose one to psychotic experiences (Hardy et al., 2017; Ruby et al., 2014). Likewise, there is a well-documented relationship between trauma and substance use, in that people with substance dependence are more likely to have experienced traumatic events (Ford et al., 2007). Among adults seeking treatment for substance use disorders, 33–50% of those meet criteria for post-traumatic stress disorder (Ralevski et al., 2014). It is speculated that some people may develop substance use disorders as they self-medicate distressing symptoms associated with a history of trauma. Future researchers should include a measure of trauma when investigating the aetiology of psychotic symptoms among those with methamphetamine-related psychosis.

Response Six

Examiner three highlighted the finding of study two "*After adjusting for confounding variables, past-year – relative to former – amphetamine users with schizophrenia were more likely to experience hallucinations in at least one sensory modality (p=0.056)*" (page 58, paragraph 3). The examiner noted that the observed p-value for this finding exceeded the predetermined alpha level of p=0.050. We choose to report on this finding (with the p-value emphasised) for several reasons. First, it has been widely argued that researchers should not rely solely on whether an effect meets some arbitrary level of statistical significance (p-values) to determine whether a difference between groups is noteworthy (Sullivan, 2012). Instead, effect size is an important metric that, unlike the p-value, indicates the magnitude of the difference between the groups. The odds ratio (2.09) for this finding indicates that those who used amphetamine in the past year had a more than two-times greater odds of experiencing hallucinations relative to those who had not used amphetamine in the past year. Not only is this finding clinically meaningful (based on the effect size), but it was directly relevant to our hypothesis: "*We expected that the prevalence rate of delusions and hallucinations to be higher in past-year – relative to former – amphetamine users with schizophrenia*". Thus, this finding contributes to the theoretical discussion around the relationship between methamphetamine use and positive psychotic symptoms among people with schizophrenia. It is important to balance both magnitude of effect and the alpha value to interpret the results.

Response Seven

Examiner three raised a comment around the specific region of dopamine dysfunction identified among people with schizophrenia. It has been hypothesised that positive psychotic symptoms may be linked to dopaminergic hyperactivity of the limbic striatum (Davis et al.,

1991; Weinberger, 1987). This hypothesis was recently examined by McCutcheon and colleagues (2018), who reviewed the existing evidence for dopaminergic abnormalities in people with schizophrenia and conducted a meta-analysis to examine the magnitude of these abnormalities across subdivisions of the striatum. It was found that those with schizophrenia display greater dopaminergic dysfunction across dorsal (rather than limbic) subdivisions of the striatum, providing evidence against a mesolimbic hypothesis of dopamine dysfunction. Molecular imaging studies have provided further evidence for the role of dopamine overactivity in the mesostriatal regions among people with schizophrenia. As highlighted by McCutcheon and colleagues (2020), there is evidence that symptoms of schizophrenia are associated with dysregulated firing of mesostriatal dopamine neurons, whereby dopamine signals may aberrantly fire with irrelevant stimuli. In theory, this could lead people with schizophrenia to experience innocuous stimuli as significant or threatening.

Response Eight

Examiner three noted that negative symptoms in study three were, on average, mild compared to the positive psychotic symptoms. The median ratings on the BPRS items for the negative-symptoms class was blunted affect (M = 2.7, SD = 1.2) emotional withdrawal (M = 2.5, SD = 1.1) and motor retardation (M = 1.6, SD = 0.7). These values fall between the BRPS ratings of very mild and mild. It is proposed that these mild negative symptoms may be artefacts of heroin and benzodiazepine use within the current sample, and it would be valuable for further research to examine the evidence of this association with more severe negative symptoms. The low severity of negative symptoms in the current sample may reflect a sampling bias, in that people with moderate or severe negative symptoms may be less likely to volunteer to participate in an interview.

Response Nine

Examiner three noted that attempts to differentiate between schizophrenia and MAP may be informed by examining whether duration of symptoms correspond to differences in the profile and severity of symptoms. A key criterion for distinguishing between MAP and SZ is duration of psychosis after cessation of drug use. Recent evidence indicates that duration of psychosis is not only associated with differences in severity of symptoms, in that those with longer lasting episodes tend to have more severe psychotic symptoms (Lecomte et al., 2013), but those with persistent episodes of psychosis exhibit a different profile of psychotic symptoms relative to those with transient symptoms. McKetin and colleagues (2017) found that methamphetamine users with persistent MAP (lasting more than one month) and those with SZ were more likely than those with transient psychosis (lasting less than one month) to experience delusions of reference, thought interference, complex auditory, visual, olfactory, and tactile hallucinations. Thus, people with transient episodes of MAP differ from people with SZ or persistent MAP, in both severity and type of psychotic symptoms. Moreover, there appear to be subtle differences in specific types of delusions and hallucinations between those with MAP and SZ, which may not have been detected by other studies (Hides et al., 2015; Medhus et al., 2013; Srisurapanont et al., 2011) that compare these disorders on broad symptom categories (e.g delusions, hallucinations). This is inconsistent with the notion that there is a linear relationship between duration and symptom profile underlying this population, and instead, there is a qualitative, rather than a purely quantitative, difference between those with persistent versus transient psychosis. In support of this hypothesis, prior research (McKetin et al., 2017) has identified different correlates associated with people who have persistent psychosis (i.e. major depression and family history of schizophrenia) from those with transient psychosis (i.e. earlier onset methamphetamine use and being male).

References

Angrist, B., & Gershon, S. (1970). The phenomenology of experimentally induced amphetamine psychosis-preliminary observations. *Biological Psychiatry, 2*, 95–107.

Barrigón, M., Diaz, F., Gurpegui, M., Ferrin, M, Salcedo, M., Moreno-Granados, J., Cervilla, J., & Ruiz-Veguilla, M. (2015). Childhood trauma as a risk factor for psychosis: A sib-pair study. *J Psychiatr Res, 70,* 130-136.

Bell, D. (1973). The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry, 29*:35–40.

Belujon, P., & Grace, A. (2017). Dopamine System Dysregulation in Major Depressive Disorders. *The international journal of neuropsychopharmacology*, *20*(12), 1036–1046.

Chang, L., Alicata, D., Ernst, T., & Volkow, N. (2007). Structural and metabolic brain changes in the striatum associated with methamphetamine abuse. *Addiction, 102*(Suppl 1):16–32.

Chen, C., Lin, S., Sham, P., Ball, D., Loh, W., & Murray, R. (2005). Morbid risk for psychiatric disorder among the relatives of methamphetamine users with and without psychosis. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, *136B*(1), 87–91.

Darke, S., Kaye, S., McKetin, R., & Duflou, J. (2008). Major physical and psychological harms of methamphetamine use. *Drug Alcohol Rev, 27*:253–262.

Davis, K., Kahn, R., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: a review and reconceptualization. *Am J Psychiatry, 148*:1474–1486.

Flaum, M., & Schultz, S. (1996). When does amphetamine-induced psychosis become schizophrenia? *Am J Psychiatry, 153*(6):812-5.

Ford, J. D., Hawke, J., Alessi, S., Ledgerwood, D., & Petry, N. (2007). Psychological trauma and PTSD symptoms as predictors of substance dependence treatment outcomes. *Behaviour Research and Therapy, 45*(10), 2417–2431.

Fraser, S., Hides, L., Philips, L., Proctor, D., & Lubman, D. (2012). Differentiating first episode substance induced and primary psychotic disorders with concurrent substance use in young people. *Schizophrenia Research, 136*(1-3):110-5.

Glasner-Edwards, S., & Mooney, L. (2014). Methamphetamine psychosis: epidemiology and management. *CNS drugs, 28*(12), 1115–1126.

Grant, K., LeVan, T., Wells, S., Li, M., Stoltenberg, S., Gendelman, H., Carlo, G., & Bevins, R. (2012). Methamphetamine-associated psychosis. *Journal Of Neuroimmune Pharmacology, 7*(1):113-39.

Hardy A. (2017). Pathways from Trauma to Psychotic Experiences: A Theoretically Informed Model of Posttraumatic Stress in Psychosis. *Frontiers in psychology*, *8*, 697.

Harley, M., Kelleher, I., Clarke, M., Lynch, F., Arseneault, L., Connor, D., & Cannon, M. (2010). Cannabis use and childhood trauma interact additively to increase the risk of psychotic symptoms in adolescence. *Psychological Medicine, 40*(10):1627–1634.

Hellem, T., Lundberg, K., & Renshaw, P. (2015). A review of treatment options for co-occurring methamphetamine use disorders and depression. *Journal of addictions nursing*, *26*(1), 14–E1.

Jan, R., Kydd, R., & Russell, B. (2012). Functional and structural brain changes associated with methamphetamine abuse. *Brain sciences*, *2*(4), 434–482.

Kendler, K., Ohlsson, H., Sundquist, J., & Sundquist, K. (2019). Prediction of onset of substance-induced psychotic disorder and its progression to schizophrenia in a Swedish national sample. *Am J Psychiatry, 176*(9):711-9.

Maia, T., & Frank, M. (2017). An integrative perspective on the role of dopamine in schizophrenia. *Biol. Psychiatry*, *81*, 52–66.

McKetin, R. (2018). Methamphetamine psychosis: insights from the past. *Addiction, 113*(8):1522-1527.

Mathias, S., Lubman, D., & Hides, L. (2008). Substance-induced psychosis: a diagnostic conundrum. *Journal of Clinical Psychiatry*, *69*(3):358-67.McKetin, R., Lubman, D., Lee, N., Ross, J. E., & Slade, T. N. (2011). Major depression among methamphetamine users entering drug treatment programs. *The Medical Journal of Australia*, *195*(3), 51 – 55.

McCutcheon, R., Beck, K., Jauhar, S., & Howes, O. (2018). Defining the locus of dopaminergic dysfunction in schizophrenia: A meta-analysis and test of the mesolimbic hypothesis. *Schizophrenia Bulletin*, *44*(6), 1301–1311.

McCutcheon, R, Marques, T., & Howes, O. (2020). Schizophrenia—An Overview. *JAMA Psychiatry*, *77*(2):201–210.

McIver, C., McGregor, C., Baigent, M., Spain, D., Newcombe, D., & Ali, R. (2006). *Guidelines for the medical management of patients with methamphetamine induced psychosis*. South Australia: Drug and Alcohol Services South Australia.

McKetin R. (2018). Methamphetamine psychosis: insights from the past. *Addiction,* 113(8):1522-1527.

McKetin, R., Lubman, D., Lee, N., Ross, J. E., & Slade, T. N. (2011). Major depression among methamphetamine users entering drug treatment programs. *Med J Aust,* 195(3): S51.

Medhus, S., Mordal, J., Holm, B., Mørland, J., & Bramness, J. (2013). A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. *Psychiatry Research, 206*(1):17-21.

Nordahl, T., Salo, R., & Leamon, M. (2003). Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. *J Neuropsychiatry Clin Neurosci, 15*(3):317-25.

Ralevski, E., Olivera-Figueroa, L., & Petrakis, I. (2014). PTSD and comorbid AUD: a review of pharmacological and alternative treatment options. *Substance abuse and rehabilitation, 5,* 25–36.

Ruby, E., Polito, S., McMahon, K., Gorovitz, M., Corcoran, C., & Malaspina, D. (2014). Pathways associating childhood trauma to the neurobiology of schizophrenia. *Front Psychol Behav Sci, 3*(1):1-17.

Shaner, A., Roberts, L., Eckman, T., Racenstein, J., Tucker, D., Tsuang, J., & Mintz, J. (1998). Sources of diagnostic uncertainty for chronically psychotic cocaine abusers. *Psychiatr Serv, 49*(5):684-90.

Sullivan, G., & Feinn, R. (2012). Using effect size-or why the p-value is not enough. *Journal of Graduate Medical Education, 4*(3), 279–282.

Sweeting, M., & Farrell, M. (2005). Metamphetamine psychosis: How is it related to schizophrenia? A review of the literature. *Current Psychiatry Reviews,* 1(2); 115-122.

Weinberger, D. (1987). Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry, 45*: 1055.

Yu, S., Zhu, L., Shen, Q., Bai, X., & Di, X. (2015). Recent advances in methamphetamine neurotoxicity mechanisms and its molecular pathophysiology. *Behavioural neurology,* 103969.

Zeidman, H., Oscherwitz, M., & Addario, D. (1975). Amphetamine psychosis or paranoid schizophrenia? *West J Med,* 122(5):394-405.

Appendix B: Supplementary Material

Supplementary Tables for Study One

A systematic review of the symptom profile and course of methamphetamine-associated psychosis

Supplementary Table 1

PRISMA Guidelines

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5 & 20
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N. A.
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N. A.
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Supp. Tables 4 - 8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	N. A.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N. A.
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N. A.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7 - 11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N. A.
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N. A.
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15 – 16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

Supplementary Table 2

Reference List of Included Studies

Reference	Study Type
Akiyama K. Longitudinal clinical course following pharmacological treatment of methamphetamine psychosis which persists after long-term abstinence. *Ann N Y Acad Sci* 2006; 1074: 125-134.	Long
Akiyama K, Saito A, Shimoda K. Chronic methamphetamine psychosis after long-term abstinence in Japanese incarcerated patients. *Am J Addict* 2011; 20(3): 240-249.	Cross
Ali R, Marsden J, Srisurapanont M, et al. Methamphetamine psychosis in Australia, Philippines, and Thailand: Recommendations for acute care and clinical inpatient management. *Addict Dis Their Treat* 2010; 9(4), 43-149.	Cross
Ånggård E, Jönsson L, Hogmark A, et al. Amphetamine metabolism in amphetamine psychosis. *Clin Pharmacol Ther* 1973; 14(5): 870-880.	Exp
Angrist B, Sathananthan G, Wilk S, Gershon S, et al. Amphetamine psychosis: Behavioral and biochemical aspects. *J Psychiatr Res* 1974; 11, 13-23.	Case
Angrist B, Gershon S. The phenomenology of experimentally induced amphetamine psychosis--preliminary observations. *Biol Psychiatry* 1970; 2(2): 95-107.	Exp
Aoki Y, Orikabe L, Takayanagi Y, et al. Volume reductions in frontopolar and left perisylvian cortices in methamphetamine induced psychosis. *Schizophr Res* 2013; 147(2-3): 355-361.	CCont
Asnafi S, Sharifi V, Tehranidoost M, et al. Negative priming in amphetamine psychosis. *Psychiatry Res* 2013; 210(1): 263.	CCont
Beamish P, Kiloh, L. Psychoses due to amphetamine consumption. *Br J Psychiatry* 1960, 106: 337-343.	Case
Bell D. Comparison of amphetamine psychosis and schizophrenia. *Br J Psychiatry* 1965; 111: 701-707.	CCont
Bell D. The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry* 1973; 29(1), 35-40.	Exp
Bergua A, Sperling W, Küchle M, et al. Self-enucleation in drug-related psychosis. *Ophthalmologica* 2002; 216(4): 269-271.	Case
Bousman C, et al. Typologies of positive psychotic symptoms in methamphetamine dependence. *Am J Addict* 2015; 24(2): 94-97.	Cross
Buffman J, Shulgin A. Overdose of 2.3 grams of intravenous methamphetamine: Case, analysis and patient perspective. *J Psychoactive Drugs* 2001; 33(4); 409-412.	Case
Carr R. Acute psychotic reaction after inhaling methylamphetamine. *Br Med J* 1954; 1(4877): 1476.	Case
Chen C, Lin S, Sham P, et al. Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychol Med* 2003; 33(8): 1407-1414.	CCont
Chen C, Lin S, Chen Y, et al. Persistence of psychotic symptoms as an indicator of cognitive impairment in methamphetamine users. *Drug Alcohol Depend* 2015; 148, 158-164.	CCont

Deng X, Huang Z, Li X, et al. Long-term follow-up of patients treated for psychotic symptoms that persist after stopping illicit drug use. *Shanghai Arch Psychiatry* 2012; 24(5): 271-278.	Long
Dore G, Sweeting A. Drug-induced psychosis associated with crystalline methamphetamine. *Australas Psychiatry* 2006; 14(1): 86-89.	Case
Ellinwood E. Amphetamine psychosis: I. Description of the individuals and process. *J Nerv Ment Dis* 1967; 144(4):273-283.	CCont
Ezaki N, Nakamura K, Sekine Y, et al. Short allele of 5-HTTLPR as a risk factor for the development of psychosis in Japanese methamphetamine abusers. *Ann N Y Acad Sci* 2008; 1139: 49-56.	CCont
Farnia V, Shakeri J, Tatari F, et al. Randomized controlled trial of aripiprazole versus risperidone for the treatment of amphetamine-induced psychosis. *Am J Drug Alcohol Abuse* 2014; 40(1): 10-15.	Cross
Fasihpour B, Molavi S, Shariat S, et al. Clinical features of inpatients with methamphetamine-induced psychosis. *J Ment Health* 2013; 22(4): 341-349.	Cross
Gold M, Bowers M. Neurobiological vulnerability to low-dose amphetamine psychosis. *Am J Psychiatry* 1978; 135(12): 1546-1548.	Case
Grelotti D, Kanayama G, Pope H, et al. Remission of persistent methamphetamine-induced psychosis after electroconvulsive therapy: Presentation of a case and review of the literature. *Am J Psychiatry* 2010; 167(1), 17-23.	Case
Griffith J, Cavanaugh J, Held J, et al. Dextroamphetamine: Evaluation of psychomimetic properties in man. *Arch Gen Psychiatry 1*972; 26(2): 97-100.	Exp
Hall R, Popkin M, Beresford T, et al. Amphetamine psychosis: clinical presentations and differential diagnosis. *Psychiatr Med* 1988; 6(1): 73-79.	Cross
Harajiri S, Kojima H, Arikawa K, et al. Synergism between methamphetamine and alcohol in a case of methamphetamine psychosis. *Kurume Medical Journal* 1986; 33(4): 163-165.	Case
Hashimoto T, Matsuzawa D, Shimizu E et al. A functional glutathione S-transferase P1 gene polymorphism is associated with methamphetamine-induced psychosis in Japanese population. *Am J Med Genet B Neuropsychiatr Genet* 2005; 135B(1): 5-9.	CCont
Herman M, Nagler S. Psychoses due to amphetamine. *J Nerv Ment Dis* 1954; 120(3-4): 268-272.	Cross
Hides L, McKetin R, Kavanagh D, et al. Primary and substance-induced psychotic disorders in methamphetamine users. *Psychiatry Res* 2015; 226(1): 91-96.	CCont
Howells F, Uhlmann A, Temmingh H, et al. (1)H-magnetic resonance spectroscopy ((1)H-MRS) in methamphetamine dependence and methamphetamine induced psychosis. *Schizophr Res* 2014; 153(1-3): 122-128.	CCont
Iwanami A, Sugiyama A, Kuroki N, et al. Patients with methamphetamine psychosis admitted to a psychiatric hospital in Japan: A preliminary report. *Acta Psychiatr Scand* 1994, 89(6), 428-432.	Cross
Iyo M, Nishio M, Itoh T, et al. Dopamine D2 and serotonin S2 receptors in susceptibility to methamphetamine psychosis detected by positron emission tomography. *Psychiatry Res* 1993; 50(4): 217-231.	CCont

Iyo M, Sekine Y, Matsunaga T, et al. (1999). Methamphetamine-associated obsessional symptoms and effective risperidone treatment: A case report. *Journal of Clinical Psychiatry* 1999; 60(5), 337-338.	Case
Javadian S, Shabani A, Shariat S, et al. Clinical course of methamphetamine-induced psychotic disorder in a 3-month follow-up. *Prim Care Companion CNS Disord* 2016, 18(6).	Long
Johnson J, Milner G. Psychiatric complications of amphetamine substances. *Acta Psychiatr Scand* 1966; 42(3): 252-263.	Cross
Jonsson L, Sjostrom K. A rating scale for evaluation of the clinical course and symptomatology in amphetamine psychosis. *Br Med J* 1970; 117(541): 661-665.	Exp
Kalayasiri R, Verachai V, Gelernter J, et al. Clinical features of methamphetamine-induced paranoia and preliminary genetic association with DBH-1021C->T in a Thai treatment cohort. *Addiction* 2014; 109(6): 965-976.	CCont
Katayama M, Onishi H, Koide S, et al. Plasma methionine enkephalin-like immunoreactivity in patients with methamphetamine psychosis. *Ann N Y Acad Sci* 1996, 801: 430-440.	CCont
Kishi T, Tsunoka T, Ikeda M, et al. Serotonin 1A receptor gene is associated with Japanese methamphetamine-induced psychosis patients. *Neuropharmacology* 2010; 58(2): 452-456.	CCont
Kittirattanapaiboon P, Mahatnirunkul S, Booncharoen H, et al. Long-term outcomes in methamphetamine psychosis patients after first hospitalisation. *Drug Alcohol Rev* 2010; 29(4): 456-461.	Long
Kratofil P, Baberg H, Dimsdale J, et al. Self-mutilation and severe self-injurious behavior associated with amphetamine psychosis. *Gen Hosp Psychiatry* 1996, 18(2), 117-120.	Case
Leamon M, Flower K, Salo R, et al. Methamphetamine and paranoia: the methamphetamine experience questionnaire. *Am J Addict* 2010, 19(2): 155-168.	CCont
Lecomte T, Mueser K, MacEwan W, et al. Predictors of persistent psychotic symptoms in persons with methamphetamine abuse receiving psychiatric treatment. *J Nerv Ment Dis* 2013; 201(12): 1085-1089.	Long
Liu X, Zhang Y, Wang X, et al. The synergistic effect of dual use of amphetamine-type stimulants and ketamine on drug-induced psychotic symptoms in Chinese synthetic drug users. *Oncotarget* 2017, 8(39): 66569-66575.	Cross
Liu H, Lin S, Liu S, et al. DAT polymorphism and diverse clinical manifestations in methamphetamine abusers. *Psychiatr Genet* 2004; 14(1): 33-37.	CCont
Lynn E. Amphetamine abuse: a speed trap. *Psychiatr Q* 1971; 45(1): 92-101.	Case
McKetin R, Baker A, Dawe S, et al. Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders. *Psychiatry Res* 2017; 251: 349-354.	CCont
McKetin R, Dawe S, Burns R, et al. The profile of psychiatric symptoms exacerbated by methamphetamine use. *Drug Alcohol Depend* 2016, 161: 104-9.	Cross
Medhus S, Mordal, J, Holm B, et al. A comparison of symptoms and drug use between patients with methamphetamine associated psychoses and patients diagnosed with schizophrenia in two acute psychiatric wards. *Psychiatry Res* 2013; 206(1): 17-21.	CCont
Medhus S, Rognli E, Gossop M, et al. Amphetamine-induced psychosis: Transition to schizophrenia and mortality in a small prospective sample. *Am J Addict* 2015; 24(7): 586-589.	Long

Mikami T, Nause N, Fukura Y, et al. Determining vulnerability to schizophrenia in methamphetamine psychosis using exploratory eye movements. *J Neuropsychiatry Clin Neurosc* 2003; 57(4): 433-440.	CCont
Misra L, Kofoed L, Oesterheld J, et al. Olanzapine treatment of methamphetamine psychosis. *Clin Psychopharmacol Neurosci* 2000; 20(3), 393-394.	Case
Nakatani Y, Hara T. Disturbance of consciousness due to methamphetamine abuse. A study of 2 patients. *Psychopathology* 1998; 31(3): 131-137.	Case
Nakatani Y, Yoshizawa J, Yamada H, et al. Methamphetamine psychosis in Japan: A survey. *Br J Addict* 1989; 84(12), 1548-1549.	Cross
Ney P. Psychosis in a child, associated with amphetamine administration. *CMAJ* 1967; 97(17): 1026-1029.	Case
Niemi-Pynttäri J, Sund R, Putkonen H, et al. Substance-induced psychoses converting into schizophrenia: A register-based study of 18,478 finnish inpatient cases. *J Clin Psychiatry* 2013; 74(1): e94-e99.	Long
O'Flanagan P, Taylor R. A case of recurrent psychosis associated with amphetamine addiction. *Br J Psych* 1950; 96(405): 1033-1036.	Case
Ohgake S, Hashimoto K, Shimizu E, et al. Functional polymorphism of the NQO2 gene is associated with methamphetamine psychosis. *Addict Biol* 2005; 10(2): 145-148.	CCont
Okahisa Y, Ujike H, Kotaka T, et al. Association between neuropeptide Y gene and its receptor Y1 gene and methamphetamine dependence. *Psychiatry Clin Neurosci* 2009; 63(3): 417-422.	CCont
Okazaki K, Makinodan M, Yamamuro K, et al. Blonanserin treatment in patients with methamphetamine-induced psychosis comorbid with intellectual disabilities. *Neuropsychiatr Dis Treat* 2016; 12: 3195–3198	Case
Omidvar T, Sharifi V. Amphetamine psychosis and eye auto enucleation. ANZJP 2012; 46(1), 71.	Case
Orikabe L, Yamasue H, Inoue H, et al. Reduced amygdala and hippocampal volumes in patients with methamphetamine psychosis. *Schizophr Res* 2011; 132(2-3): 183-189.	CCont
Perry P, Juhl R. Amphetamine psychosis. *Am J Hosp Pharm* 1977; 34(8): 883-885.	Case
Prout C. Reactions to use of amphetamine as observed in a psychiatric hospital. *N Y State J Med* 1964; 64: 1186-1192.	Case
Rickman E, Williams E, Brown R, et al. Acute toxic psychiatric reactions related to amphetamine medication. *Med Ann Dist Columbia* 1961; 30: 209-212.	Cross
Salo R, Fassbender C, Iosif A, et al. Predictors of methamphetamine psychosis: history of ADHD-relevant childhood behaviors and drug exposure. *Psychiatry Res* 2013; 210(2): 529-535.	CCont
Sato M, Chen C, Akiyama K, et al. Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biol Psychiatry* 1983; 18(4), 429-440.	Long
Sato M. Acute exacerbation of methamphetamine psychosis and lasting dopaminergic supersensitivity--a clinical survey. *Psychopharmacol Bull* 1986; 22(3): 751-756.	Cross
Schulz S, Schulz P, Dommisse C, et al. Amphetamine response in borderline patients. *Psychiatry Res* 1985; 15(2): 97-108.	Exp
Shelly J, Uhlmann A, Sinclair H, et al. First-rank symptoms in methamphetamine psychosis and schizophrenia. *Psychopathology* 2016; 49(6): 429-435.	CCont

Siomopoulos V. Thought disorder in amphetamine psychosis: a case report. *Psychosomatics 1976; 17(1): 42-44.*	Case
Srisurapanont M, Ali R, Marsden J, et al. Psychotic symptoms in methamphetamine psychotic in-patients. *Int J Neuropsychopharmacol* 2003; 6(4): 347-352.	Cross
Srisurapanont M, Arunpongpaisal S, Wada K, et al. (2011). Comparisons of methamphetamine psychotic and schizophrenic symptoms: a differential item functioning analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2011; 35(4): 959-964.	CCont
Stanciu C, Penders T, Oxentine H, et al. Delusional infestation following misuse of prescription stimulants. *Psychosomatics 2*015; 56(2), 210-212.	Case
Sulaiman A, Gill J, Said M, et al. An open-label study of aripiprazole for methamphetamine induced psychosis. *J Clin Psychopharmaco* 2012; 22(2), 121-129.	Cross
Suzuki A, Nakamura K, Sekine Y, et al. An association study between catechol-O-methyl transferase gene polymorphism and methamphetamine psychotic disorder. *Psychiatr Genet* 2006; 16(4): 133-138.	CCont
Szuster R. Methamphetamine in psychiatric emergencies. *Hawaii Med J* 1990; 49(10): 389-391.	Cross
Tomiyama G. Chronic schizophrenia-like states in methamphetamine psychosis. *Psychiatry Clin Neurosci* 1990; 44(3): 531-539.	Long
Twohig M, Varra E. Treatment of drug-induced stereotypy. *Behav Analy Today* 2006, 7(2), 206-211.	Case
Verachai V, Runkngan W, Chawanakrasaesin K, et al. Treatment of methamphetamine-induced psychosis: a double-blind randomized controlled trial comparing haloperidol and quetiapine. *Psychopharmacology* 2014; 231(16): 3099-3108.	Cross
Vila-Rodriguez F, Macewan, W, Honer, W, et al. Methamphetamine, perceptual disturbances, and the peripheral drift illusion. *The Am J Addict* 2011; 20(5), 490.	Case
Wallis G, McHarg J, Scott O, et al. Acute psychosis caused by dextro-amphetamine. *Br Med J* 1949; 2(4641): 1394.	Case
Wang G, Devi Thakoor J, Wang X, et al. Severe exacerbation of psychosis after sudden withdrawal of chlorpromazine in the treatment of methamphetamine-associated psychosis with aripiprazole and chlorpromazine: 2 case reports. *J Addict Med* 2014; 8(6), 479-481.	Case
Yeh H, Lee Y, Sun H, et al. Six months follow-up of patients with methamphetamine psychosis. *Chinese Medical Journal* 2001; 64(7): 388-394.	Long
Yeh T, Lin Y, Chen L, et al. (2014). Aripiprazole treatment in a case of amphetamine-induced delusional infestation. *ANZJP* 2014; 48(7), 681-682.	Case
Yokobayashi E, Ujike H, Kotaka T, et al. Association study of serine racemase gene with methamphetamine psychosis. *Curr Neuropharmacol* 2011; 9(1), 169-175.	CCont
Young G, Simson C, Frohman C, et al. Clinical and biochemical studies of an amphetamine withdrawal psychosis. *J Nerv Ment Dis* 1961; 132: 234-238.	Case
Yui K, Goto K, Ikemoto S, et al. Monoamine neurotransmitter metabolites and spontaneous recurrence of methamphetamine psychosis. *Brain Res Bull* 1997; 43(1): 25-33.	CCont
Yukitake A. Amphetamine psychosis in Tokyo--its clinical features and social problems. *Folia Psychiatr Neurol Jpn* 1983; 37(2): 115-120.	Cross

Zarrabi H, Khalkhali M, Hamidi A, et al. Clinical features, course and treatment of methamphetamine-induced psychosis in psychiatric inpatients. *BMC Psychiatry* 2016; 16(44).	Cross
Zeidman H, Oscherwitz M, Addario D, et al. Amphetamine psychosis or paranoid schizophrenia? *West J Med* 1975; 122(5): 394-405.	Case
Zhang K, Zhang K, Zhao Y, et al. Association study of GABA system genes polymorphisms with amphetamine-induced psychotic disorder in a Han Chinese population. *Neurosci Lett* 2016; 622: 37–44.	Ccont

Note. CCont = Case control study (*k*=29), Cross = Cross-sectional study (*k*=20), Long = Longitudinal study (*k*=10), Exp = Experimental study (*k*=6), Case = Case study (*k*=29). List of excluded studies with justifications available from author upon request.

Supplementary Table 3

Sample Characteristics and Clinical Symptoms Reported in Case Control Studies (k=29)

First author, year, and country	*N*	Mean age in years (± SD) [1]	Male (%)	Substance	Dependence (%)	Symptom scale	MAP diagnosis / identification method.	Symptoms reported as present and absent (prevalence where available) [2]	Proportion with persistent psychosis (%)
Aoki, 2013, Japan	20	34 ± 7.8	*NR*	Meth	*NR*	BPRS	Diagnosis * interview (ICD-10 and DSM-IV).	Negative symptoms.	*NR*
Asnafi, 2013, Iran	19	33 ± 5.0	79	Amph	*NR*	BPRS	Diagnosis * interview (DSM-IV and SCID Persian version)	Persecutory D, Grandiose D, Flat Affect, Reduced Movement, Stereotyped Behaviour	*NR*
Bell, 1965, Australia	7	*NR*	*NR*	Amph	*NR*	*NR*	Identified * MAP if symptomatic and using methamphetamine, interview and observation.	Persecutory D, Reference D, Control D, Visual H, Auditory H, Depression, Suicidality, Self-harm, Mania, Hostility, Conceptual Disorganisation (0%) Flat affect.	0
Chen, 2003, Taiwan	174	27 ± 7.1	74	Meth	*NR*	DIGS (C)	Diagnosis * interview and urine testing (DISG-C and DSM-IV)	Persecutory D (71%) Reference D (63%) Somatic D (11%) Guilt D (15%) Grandiose D (12%) Jealous D (20%) Broadcasting D (26%) Insertion D (28%) Withdrawal D (19%) Control D (23%) Mindreading D (41%) Visual H (46%) Auditory H (84%) Tactile H (21%) Olfactory H (18%) Gustatory H (12%) Inappropriate affect (12%) Disorganised Behaviour (27%) Avolition (15%) Flat affect	39

								(18%) Reduced movement (7%)	
Chen, 2015, Taiwan	106	35 ; 37[3]	79	Meth	100	BPRS	Diagnosis # * urine testing and interview (DISG-C and DSM-IV)	Negative symptoms	*NR*
Ellinwood, 1967, USA	10	Range: 18-41	40	Amph	100	*NR*	Identified * MAP if symptomatic and using methamphetamine, interview and observation	Persecutory D (100%), Reference D (100%) Visual H (100%) Auditory H (100%) Tactile H (70%) Olfactory H (70%) Depression (50%) Anxiety (70%), Hostility (30%), Disorientation, Suicidality (10%), Religious, Self Harm (30%), Control D.	*NR*
Ezaki, 2008, Japan	166	37 ± 11.0	83	Meth	100	*NR*	Diagnosis * medical records and interview (ICD-10-DCR)	*NR*	42
Hashimoto, 2005, Japan	189	37 ± 12	78	Meth	100	*NR*	Diagnosis * medical records and interview (ICD-10-DCR)	*NR*	41
Hides, 2015, Australia	49	30	65	Meth	67	BPRS	Diagnosis ^ interview, PRISM-IV Version 6 (DSM-IV)	Depression, Anxiety, Mania	*NR*
Howells, 2014, Cape Town	10	24 ± 5.7	90	Meth	100	PANSS	Identified * MAP if dependant and symptomatic, interview and observation	Negative symptoms	*NR*
Iyo, 1993, Japan	6	28 ± 2.8	100	Meth	*NR*	*NR*	Diagnosis, interview (DSM-III-R)	Persecutory D, Broadcasting D, Insertion D, Withdrawal D, Control D, Mindreading D, Visual H, Auditory H, Conceptual Disorganisation (0%)	*NR*
Kalayasiri, 2014, Thailand	289	Range: 18-28	49	Meth	92	*NR*	Identified + MAP if dependant and symptomatic, interview and observation	Visual H (65%) Auditory H (28%) Tactile H (12%) Olfactory H (4%)	*NR*
Katayama, 1996, Japan	9	36 ± 5.4	100	Meth	*NR*	BPRS	Identified, MAP if using methamphetamine and symptomatic, interview and observation	Persecutory D, Conceptual Disorganisation.	*NR*

Kishi, 2010, Japan	197	37 ± 12.2	83	Meth	100	*NR*	Diagnosis, medical records and interview (DSM-IV)	NR	43
Leamon, 2010, USA	123	37 ± 9.1	61	Meth	100	MEQ	Identified ^ MAP if using methamphetamine and symptomatic, interview	Persecutory D (86%), Visual H (67%) Auditory H (63%) Tactile H (37%)	*NR*
Liu, 2004, Taiwan	116	29	91	Meth	100	*NR*	Identified *# MAP if dependant and symptomatic, medical records and observation	*NR*	24
McKetin, 2017, Australia	122	32 ± 8.2	71	Meth	100	CIDI	Diagnosis + and interview (DSM-IV)	Persecutory D (85%), Reference D (23%), Jealous D (27%), Control D (17%), Mindreading (17%), Broadcasting D (28%), Insertion D (22%), Visual H (56%), Auditory H, Tactile H (56%), Olfactory H (28%), Gustatory H (21%).	30
Medhus, 2013, Norway	9	Mean (range): 33 (30–36)	71	Meth + Amph	*NR*	PANSS	Diagnosis * blood testing and interview (ICD-10)	Persecutory D, Grandiose D, Conceptual disorganisation, Inappropriate affect, Hostility.	*NR*
Mikami, 2003, Japan	48	33 ± 8.5	70	Meth	*NR*	*NR*	Diagnosis * interview (DSM-IV)	Negative Symptoms	37.5
Ohgake, 2005, Japan	191	37 ± 10.6	79	Meth	100	*NR*	Diagnosis * interview (ICD-10-DCR)	*NR*	45
Okahisa, 2009, Japan	222	37 ± 11.9	79	Meth	100	*NR*	Diagnosis * interview (ICD-10)	*NR*	44
Orikabe, 2011, Japan	20	Mean: 34 range: 22-52	50	Meth	*NR*	BPRS	Diagnosis * interview (ICD-10)	Negative symptoms	*NR*
Salo, 2013, USA	145	38 ± 8.2	54	Meth	100	MEQ	Diagnosis + interview (DSM-IV)	Visual H, Auditory H	*NR*
Shelly, 2016, Cape Town	33	IQR: 18-34	24	Meth	*NR*	SCID	Diagnosis*+ interview (DSM-IV)	Broadcasting D, Insertion D, Withdrawal D, Control D, Auditory H.	*NR*
Srisurapanont, 2011, Australia, Japan,	168	27 ± 7.6	76	Meth	*NR*	Manchester	Diagnosis * interview using MINI-Plus Module M (ICD-10 and DSM-IV)	Depression, Anxiety, Flat affect, Disorganised Speech,	*NR*

Philippines, Thailand								Poverty of Speech, Stereotyped Behaviour, Negative Symptoms	
Suzuki, 2006, Japan	143	36 ± 11	81	Meth	100	*NR*	Diagnosis * medical records and interview (ICD-10)	*NR*	45
Yokobayashi , 2011, Japan	225	37 ± 11.9	80	Meth	100	*NR*	Diagnosis * medical records and interview (ICD-10)	*NR*	44
Yui, 1997, Japan	50	Mean: 25 - 29	0	Meth	*NR*	*NR*	Diagnosis # medical records and interview (DSM-III-V)	Persecutory D, Reference D, Auditory H, Visual H.	*NR*
Zhang, 2016, China	400	36 ± 8.5	84	Amph	*NR*	*NR*	Diagnosis * medical records and interview (DSM-IV)	Reference D (42%), Persecutory D (42%), Jealousy D (40%), Control D (36%), Grandiose D (23%), Auditory H (79%), Visual H (42%), Tactile H (35%).	*NR*

Note. *NR* = Not reported or unclear; H = hallucinations; D = delusions; * = participants recruited from hospital inpatient/outpatient samples; # = participants recruited from prison; ^ = participants recruited from community; + = participants recruited from treatment centres; recruitment method not reported or unclear where blank; 1. Age is years is presented as sample mean with standard deviation or as a range; 2. Symptoms explicitly reported as absent are denoted with “Symptom (0%)”; 3. Two mean ages are provided as this paper contained two MAP samples. Meth = methamphetamine; Amph = amphetamine. The terms ‘amphetamine’ and ‘methamphetamine’ (and the associated street names) have been used interchangeably or inconsistently, and may not reflect forensically verified differences in chemical structure.

Supplementary Table 4

Sample Characteristics and Clinical Symptoms Reported for Cross Sectional Studies (k=20)

First author, year, and country	*N*	Mean age in years (±SD) [1]	Male (%)	Substance	Dependent (%)	Symptom scale	MAP diagnosis / identification method.	Symptoms reported as present (prevalence where available) [2]	Persistent psychosis (%)
Akiyama, 2011, Japan	80	32 ±7.5	0	Meth	100	BPRS	Identified # MAP if dependant and symptomatic, based on interview	Persecutory D (82%) Broadcasting D (61%) Visual H (53%) Auditory H (81%) Tactile H (33%) Depression (83%) Suicidality (62%) Hostility (84%) Inappropriate affect, Negative symptoms.	*NR*
Ali, 2010, Australia, Philippines, Thailand	150	26 ±6.3	79	Meth + Amph	87	Manch-ester	Diagnosis *+ interview using MINI-Plus Module M (ICD-10 and DSM-IV)	Persecutory D (81%) Reference D (42%) Insertion D (38%) Mindreading D (60%) Visual H (40%) Auditory H (76%) Disorganised Behaviour (10%) Disorganised Speech (12%) Negative symptoms (26%)	*NR*
Bousman, 2015, Australia	40	39 ±10	95	Meth	100	MINI adapted	Identified ^ MAP if dependant and symptomatic, based on interview	Persecutory D (88%) Insertion D (33%) Withdrawal D (28%) Control D (38%), Mindreading D (40%), Visual H (63%), Auditory H (60%)	*NR*
Farnia, 2014, Iran	45	Mean: 40 Range: 26–60	100	Amph	*NR*	SANS & SAPS	Diagnosis * interview (DSM-IV)	Disorganised Behaviour, Conceptual Disorganisation, Flat affect, Poverty of Speech, Avolition.	*NR*
Fasihpour, 2013, Iran	111	30 ±7.5	95	Prescript Amph	*NR*	*NR*	Diagnosis * medical records (based on DSM-IV criteria)	Persecutory D (82%) Reference D (57%) Somatic D (4%) Grandiose D (40%) Jealous D (26%) Broadcasting D (6%) Insertion D (2%) Withdrawal D (4%) Control D (4%) Visual H (44%) Auditory H (70%) Tactile H (2%) Olfactory H (1%)	9%
Hall, 1988, USA	11	*IQR*: 15-30	*NR*	Amph	*NR*	*NR*	Identified * MAP if using methamphetamine and symptomatic, interview with relatives and participant, urine testing.	Persecutory D (81%) Reference D (100%) Control D (72%) Visual H (18%) Auditory H (54%) Tactile H (18%) Olfactory H (0%) Depression (90%) Anxiety (63%) Hostility (27%) Inappropriate affect (9%) Conceptual Disorganisation (18%) Disorganised	*NR*

							Behaviour (90%) Stereotyped Behaviour (0%) Flat affect (9%) Disorientation (36%) Reduced movement (9%)	
Herman, 1954, USA	8	30	87	Prescript Amph	*NR*	*NR*	Identified, MAP if symptomatic and using methamphetamine, urine testing and observation.	Persecutory D, Auditory H (87%) Inappropriate affect, Disorientation.	*NR*
Iwanami, 1994, Japan	104	35	80	Meth	*NR*	*NR*	Diagnosis * urine testing and interview (DSM-III-R)	Persecutory D (83%) Reference D (85%) Visual H (25%) Auditory H (72%) Depression (90%) Anxiety (63%) Hostility (27%) Inappropriate affect (100%) Conceptual Disorganisation (18%) Disorganised Behaviour (90%) Flat affect (9%) Disorientation (36%)	26
Johnson, 1966, Britain	17	35	28	Amph	*NR*	*NR*	Identified * MAP if symptomatic and using methamphetamine or dependant, observation, urine testing and medical records	Depression, Hostility, Conceptual Disorganisation	*NR*
Liu, 2017, China	150	13-36	99	Meth + Amph	*NR*	*BPRS*	Diagnosis+ and interview (ICD-10)	Persecutory D, Conceptual Disorganisation, Hostility, Depression, Anxiety, Hyperactivity.	*NR*
McKetin, 2016, Australia	164	32±8.2	60	Meth + Amph	100	BPRS	Diagnosis + and interview (DSM-IV)	Persecutory D, Guilt D, Grandiose D, Conceptual Disorganisation, Anxiety, Depression, Suicidality, Hostility, Mania, Inappropriate affect, Hyperactivity, Disorientation, Disorganised Behaviour, Flat affect, Social withdrawal, Reduced movement	*NR*
Nakatani, 1989, Japan	132	33	79	Meth	*NR*	*NR*	Previously diagnosed * as MAP in medical records.	Auditory H	*NR*
Rickman, 1961, USA	18	*NR*	11	Prescript Amph	*NR*	*NR*	*NR* *	Persecutory D, Visual H, Depression	*NR*
Sato, 1986, Japan	21	*NR*	75	Meth	*NR*	*NR*	Identified * MAP if symptomatic and using, observation, urine testing and medical records.	Persecutory D, Broadcasting D, Visual H, Auditory H, Anxiety, Hostility, Inappropriate affect, Conceptual Disorganisation, Disorganised Behaviour	18

Srisurapanont, 2003, Australia, Japan, Philippines Thailand	168	27 ±7.6	76	Meth	*NR*	MINI Plus	Diagnosis * interview using MINI-Plus Module M (ICD-10 and DSM-IV)	Persecutory D (77%) Reference D (38%) Insertion D (33%) Mindreading D (53%) Visual H (38%) Auditory H (73%) Disorganised Behaviour (8%) Disorganised Speech (11%) Negative symptoms (21%)	*NR*
Sulaiman, 2012, Malaysia	49	34 ±8.4	94	Meth	100	PANSS	Diagnosis * urine testing and interview using MINI (DSM-IV)	Negative Symptoms	0
Szuster, 1990, Hawaii	14	IQR: 21-40	78	Meth	*NR*	*NR*	Identified * MAP if dependant and previously identified in medical records.	Persecutory D (86%) Visual H (35%) Auditory H (64%) Suicidality (29%) Self-harm (7%) Hostility (43%)	*NR*
Verachai, 2014, Thailand	80	23 & 25[3]	70, 83[3]	Meth	100	PANSS	Diagnosis + interview (classification NR)	Negative Symptoms	*NR*
Yukitake, 1983, Japan	60	Mean: 30 Range: 19-49	86	Meth + Amph	*NR*	*NR*	*NR* *	Persecutory D, Reference D, Grandiose D, Visual H, Auditory H, Suicidality, Self-harm, Hostility, Inappropriate affect, Disorganised Behaviour, Disorganised Speech, Disorientation	*NR*
Zarrabi, 2016, Iran	152	36 ±8.1	94	Meth	*NR*	*BPRS*	Diagnosis * urine testing and interview (DSM-IV)	Persecutory D (85%), Reference D (39%), Grandiosity D (33%), Jealousy D (30%), Broadcasting D (1%), Insertion D (1%), Withdrawal D (1%), Auditory H (51%), Visual H (18%), Tactile H (1%), Hostility (69%), Suicidality (14%).	32

Note. *NR* = Not reported or unclear; H = hallucinations; D = delusions; * = participants recruited from hospital inpatient/outpatient samples; # = participants recruited from prison; ^ = participants recruited from community; + = participants recruited from treatment centres; recruitment method not reported or unclear where blank. 1. Age is years is presented as sample mean with standard deviation or as a range; 2. Symptoms explicitly reported as absent are denoted with "Symptom (0%)"; 3. Two values are provided as this paper contained two MAP samples. Amph= Amphetamine. Meth = Methamphetamine. Prescript Amph = Prescription Amphetamines (for example, dextroamphetamine or d-amphetamine). The terms 'amphetamine' and 'methamphetamine' (and the associated street names) have been used interchangeably or inconsistently, and may not reflect forensically verified differences in chemical structure.

Supplementary Table 5

Sample Characteristics and Clinical Symptoms Reported in Experimental Studies (k=6)

Lead author, year and country	*N*	Age range in years	% Male	Screened for PPD	Dose, time frame, substance	Symptoms reported as present or absent (prevalence in sample were available) [2]	Duration symptoms after drug cessation
Anggard, 1973, Sweden	11	24-41	100	N*	50mgs, every six hours, over 18 hours. Prescript Amph	*NR*	1 week or less for all participants, mean 5.3 days
Angrist, 1970, USA	4	23-33	75	Y	5-50mgs hourly for 2-3 days. Prescript Amph	Persecutory D (100%), Control D (50%), Olfactory H (25%), Auditory H (50%), Inappropriate affect (50%), Flat affect (25%), Hostility (75%), Social Withdrawal D (25%), Depression (50%), Anxiety (25%), Disorganised Speech (50%), Tactile H (25%), Hyperactivity (25%), Grandiose D (25%), Disorganised Behaviour (25%).	<2 days for all participants
Bell, 1973, Australia	13	16-39	77	Y[1] *	274mgs (Mean) injected over 2-3 hrs. Prescript Amph	Persecutory D (100%), Visual H (61%), Auditory H (76%), Tactile H, Anxiety, Hostility, Inappropriate affect, Hyperactivity, Disorganised Speech (30%), Poverty of Speech, Conceptual Disorganisation (0%), Reduced movement.	1-2 days in 9 participants, 6 days in 2 participants
Griffith, 1972, USA	9	21-37	100	N*	10mgs every hour until psychosis (max 5 days). Prescript Amph	Persecutory D, Reference D, Control D, Visual H (0%), Auditory H (0%), Olfactory H, Avolition, Hostility, Hyperactivity, Social Withdrawal D, Disorientation (0%), Flat affect, Conceptual Disorganisation (0%).	<12 hours for all participants
Jonsson, 1970, Sweden	15	18-35	86	N*	50-75mgs every 6 hours, for 36 hours. Amph	Persecutory D (100%), Depression (66%), Anxiety (86%), Hostility (13%), Hyperactivity (100%), Disorientation (46%), Conceptual Disorganisation (93%), Disorganised Behaviour (46%).	<5 days for all participants
Schulz, 1985, USA	8	19-37	0	Y*	30mgs one-off. Prescript Amph	Mania, Conceptual Disorganisation, Disorganised Speech, Thought Broadcasting D, Auditory H, Visual H.	<1 day for all participants

Note. *NR* = Not reported or unclear; PPD = Primary psychotic disorders, such as schizophrenia or bipolar disorder. 1. Bell (1973) included individuals diagnosed with schizophrenia in results presented separately from those with MAP. H = hallucinations; D = delusions; * = participants recruited from hospital inpatient/outpatient samples; recruitment method not reported or unclear where blank. 2. Symptoms explicitly reported as absent are denoted with "Symptom (0%)". Amph= Amphetamine. Prescript Amph = Prescription Amphetamines (for example, dextroamphetamine or d-amphetamine). The terms 'amphetamine' and 'methamphetamine' (and the associated street names) have been used interchangeably or inconsistently, and may not reflect forensically verified differences in chemical structure.

Supplementary Table 6

Sample Characteristics and Clinical Symptoms Reported for Longitudinal Studies (k=10)

First author, year, and country	*N* (% at follow up)	Max follow up length in months	Age in years mean ± SD (or range)	Substance	Male (%)	Scale used for symptoms	Diagnosed or identified as MAP, method and classification system used (if app.)	Symptoms reported as present or absent (prevalence in sample were available)	Persistent psychosis (%)	Longitudinal outcome
Akiyama, 2006, Japan	32 (97%)	120	Range: 20-40	Meth	0	BPRS	Identified # MAP if dependant and symptomatic, interview	Persecutory D (91%), Auditory H (91%), Thought Broadcasting D (75%), Visual H (69%), Tactile H (41%), Depression (91%), Suicidality (69%).	96%	*NR*
Deng, 2012, China	38 (100%)	108	24 ±8.3	Meth	85	PANSS	Diagnosis * interview (CCMD-3)	None	21%	*NR*
Javadian, 2016, Iran	50 (92%)	3	35±8.2	Meth	86	SANS, SAPS	Diagnosis * interview (DSM-IV)	Delusions, Hallucinations, Negative Symptoms, Depression, Mania	*NR*	Depression increased, no change in negative symptoms, and reduction in delusions, hallucinations and mania.
Kittirattanapaiboon, 2010, Thailand	1116 (40%)	84	33 ±8.0	Meth	91	MINI	Diagnosis * interview, MINI (DSM-IV)	None	14%	38% transitioned to schizophrenia
Lecomte, 2013, Canada	295 (54%)	6	Means: 33; 38[1]	Meth	53	BPRS	Identified *^+ MAP if symptomatic and dependant, interview	None	30%	*NR*
Medhus, 2015, Norway	28 (43%)	72	Means: 36; 34[1]	Meth + Amph	83	PANSS	Diagnosis * based on DSM-IV (process NR), blood and urine testing	Conceptual disorganisation, Inappropriate affect, Grandiose D, Persecutory D, Hostility.	*NR*	33% transitioned to schizophrenia

Niemi-Pynttäri, 2013, Finland	825 (100%)	192	26 ±7.8	Meth + Amph	74	*NR*	Previously identified * as MAP in medical records (DSM-III-R before 1995, ICD-10 afterwards)	None	*NR*	16% transitioned to schizophrenia
Sato, 1983, Japan	21 (76%)	36	31	Meth	94	*NR*	Identified * MAP if symptomatic and using methamphetamine, urine testing, medical records and observation	Control D + Thought Insertion D + Thought Broadcasting D (24%), Persecutory D + Jealous D (100%), Auditory H (76%), Visual H (38%), Disorganised Speech + Conceptual Disorganisation (19%).	*NR*	No change in baseline symptoms over time.
Tomiyama, 1990, Japan	11 (100%)	4	39 ±10.2	Meth	82	SANS	*NR* *	Persecutory D & Reference D (63%) Broadcasting D (9%) Control D (36%) Visual H (45%) Auditory H (100%), Hyperactivity, Avolition, Flat Affect, Poverty of Speech, Reduced movement	*NR*	Positive symptoms reduced. Increase in Flat Affect, Reduced Movement, Social Withdrawal D, Conceptual Disorganisation.
Yeh, 2001, Taiwan	21 (81%)	7	31 ±1.6	Meth + Amph	90	SADS & SANS	Identified * MAP if symptomatic and using methamphetamine, interview, urine testing, observation	Persecutory D, Reference D, Thought Broadcasting D, Auditory H, Flat Affect, Poverty of Speech, Avolition, Social Withdrawal.	*NR*	Decrease in Persecutory D, Thought Broadcasting D, Auditory H, and Social Withdrawal. No change in Reference D, Flat Affect, Poverty of Speech, Avolition.

Note. *NR* = Not reported or unclear; H = hallucinations; D = delusions; * = participants recruited from hospital inpatient/outpatient samples; # = participants recruited from prison; ^ = participants recruited from community; + = participants recruited from treatment centres; recruitment method not reported or unclear where blank. 1. Two values are provided as this paper contained two MAP samples. Amph= Amphetamine. Meth = Methamphetamine. The terms ‘amphetamine’ and ‘methamphetamine’ (and the associated street names) have been used interchangeably or inconsistently, and may not reflect forensically verified differences in chemical structure.

Supplementary Table 7

Sample Characteristics and Clinical Symptoms Reported for Case Studies (29 case reports with 49 individual cases)

Lead author, year, and country	Case #	Age	Sex	Substance	Symptoms reported as present or absent [1]	Duration of symptoms
Angrist, 1974, USA	1 *	19	M	Amph	Persecutory D, Reference D, Visual H, Hyperactivity	NR
	2 *	18	M	Amph	Reference D, Grandiose D, Disorganised Speech, Conceptual Disorganisation	*NR*
	3 *	18	M	Amph	Persecutory D, Reference D, Auditory H, Anxiety, Hostility, Disorganised Speech, Conceptual Disorganisation	*NR*
	4 *	*NR*	M	Prescript Amph	Persecutory D, Reference D, Visual H, No Auditory H, Anxiety, Hostility	*NR*
Beamish, 1960, England	1 *	35	M	Prescript Amph	Persecutory D, Guilt D, Visual H, Auditory H, Depression, Suicidality, Hostility, Flat Affect, Inappropriate Affect	*NR*
	2 *	39	M	Prescript Amph	Persecutory D, Reference D, Visual H, Auditory H	*NR*
	3 *	32	F	Prescript Amph	Persecutory D, Visual H, Depression, Suicidality, Hostility, Social Withdrawal, Disorientation, Hyperactivity	<1 week
	4 *	35	M	Prescript Amph	Jealous, Hostility, Social Withdrawal, Disorganised Speech, No Conceptual Disorganisation	<1 week
	5 *	30	M	Prescript Amph	Persecutory D, Hostility, Disorganised Speech, Conceptual Disorganisation, Inappropriate Affect, Hyperactivity	<1 week
	6 *	19	F	Prescript Amph	Visual H, Auditory H, Anxiety, Disorientation, Conceptual Disorganisation, Hyperactivity	*NR*
Bergua, 2002, Germany	Single *	28	M	Amph	Guilt D, Grandiose D, Religious, Self Harm	1-6 months
Buffman, 2001, USA	Single +	34	M	Meth	Visual H, Auditory H, Inappropriate Affect, Disorientation, Hostility, Depression, Disorganised Speech	1-4 weeks
Carr, 1954, England	Single *	41	M	Meth	Persecutory D, Visual H, Auditory H, Anxiety, Disorientation	< 1 week
Dore, 2006, Australia	Single *	44	F	Meth	Persecutory D, Reference D, Visual H, Auditory H, Self Harm, NO Disorientation	*NR*
Gold, 1978, USA	Single *	20	F	Prescript Amph	Persecutory D, Reference D, Grandiose D, Visual H, Depression, Anxiety, Social Withdrawal, Disorganised Speech, Poverty of Speech, Conceptual Disorganisation, Hyperactivity, Stereotyped Behaviour	1-4 weeks

Grelotti, 2010, USA	Single *	37	M	Meth	Persecutory D, Visual H, Auditory H, Depression, Suicidality, Social Withdrawal	1-4 weeks
Harajiri, 1986, Japan	Single *	25	M	Prescript Amph	Visual H, Auditory H, Depression, Anxiety, Self-Harm, Hostility, Social Withdrawal, NO Disorientation, Conceptual Disorganisation, Hyperactivity	*NR*
Iyo, 1999, Japan	Single *	24	M	Meth	Persecutory D, Auditory H	*NR*
Kratofil, 1996, USA	1 *	31	M	Amph	Persecutory D, Religious, Auditory H, Self-Harm	*NR*
	2 *	29	M	Meth	Persecutory D, Self-Harm	*NR*
	3 *	27	M	Amph	Persecutory D, Somatic D, Grandiose D, Religious, Self-Harm	*NR*
Lynn, 1971, USA	1 *	25	M	Prescript Amph	Persecutory D, Visual H, Hostility, NO Disorientation, NO Conceptual Disorganisation, Inappropriate affect, Hyperactivity, Stereotyped Behaviour	1-4 weeks
	2 *	29	F	Prescript Amph	Visual H, Auditory H, Anxiety, NO Disorientation, NO Conceptual Disorganisation, Inappropriate affect	<1 week
	3 *	24	F	Meth	Persecutory D, Somatic D, Visual H, Auditory H, Anxiety, Hostility, NO Disorientation, Conceptual Disorganisation, Inappropriate affect	*NR*
	4 *	38	F	Prescript Amph	Persecutory D, Anxiety, Hostility, NO Disorientation, NO Conceptual Disorganisation, NO Disorganised Behaviour, NO Stereotyped Behaviour	*NR*
	5 *	50	F	Meth	Somatic D, NO Hallucinations (Vis, Aud, Olf, Tact, Gust), NO Disorientation, Flat affect, Conceptual Disorganisation, Inappropriate affect, Hyperactivity, Disorganised Behaviour	1-4 weeks
Misra, 2000, USA	Single *	50	M	Meth	Persecutory D, Visual H, Auditory H, Hostility	*NR*
Nakatani, 1998, Japan	1 *	55	M	Meth	Somatic D, Tactile H, Conceptual Disorganisation, Hostility, Hyperactivity, NO Disorientation	1-4 weeks
	2 *	47	M	Meth	Conceptual Disorganisation, Hostility, Auditory H, Visual H, Persecutory D, Disorientation	< 1 week
Ney, 1967, Canada	Single ~	8	M	Prescript Amph	Persecutory D, Reference D, Visual H, Auditory H, Tactile H, NO Depression, NO Anxiety, Hyperactivity	*NR*
O'Flanagan, 1950, England	Single *	38	M	Prescript Amph	Persecutory D, Somatic D, NO Hallucinations (Vis, Aud, Olf, Tact, Gust), Depression, Mania, NO Disorientation, Disorganised Speech, Hyperactivity	< 1 week
Okazaki, 2016, Japan	1~	25	F	Meth	Visual H, Auditory H, Self-harm	>6 months
	2~	24	F	Meth	Persecutory D, Hostility, Hyperactivity	1-4 weeks
Omidvar, 2012, Iran	Single *	47	M	Meth	Persecutory D, Control D, Depression, Self Harm, Social Withdrawal	*NR*
Perry, 1977, USA	Single *	16	F	Prescript Amph	Grandiose D, Religious, Auditory H, Hostility, Stereotyped Behaviour,	1-4 weeks

Prout,1964, USA	1 *	50	F	Prescript Amph	Depression, Hostility, Disorganised Speech, Inappropriate Affect	*NR*
	2 *	28	F	Prescript Amph	Persecutory D, Reference D, Visual H, Auditory H, Hostility, Social Withdrawal, Hyperactivity, Inappropriate Affect	*NR*
	3 *	23	F	Prescript Amph	Persecutory D, Auditory H, Depression, Suicidality, Hostility, Hyperactivity	*NR*
Siomopoulos, 1976, USA	Single *	29	M	Prescript Amph	Persecutory D, Grandiose D, NO Hallucinations (Vis, Aud, Olf, Tact, Gust), Anxiety, NO Disorientation, NO Disorganised Speech, NO Poverty of Speech, Conceptual Disorganisation, Stereotyped Behaviour	*NR*
Stanciu, 2015, USA	Single *	30	F	Prescript Amph	Somatic D, Tactile H, Anxiety, Self-harm, Hostility, Hyperactivity	1-4 weeks
Twohig, 2006, USA	Single *	*NR*	M	Meth	Persecutory D, Visual H, Hostility, Stereotyped Behaviour	*NR*
Vila-Rodriguez, 2011, Canada	Single	35	M	Meth	Visual H, Persecutory D	*NR*
Wallis, 1949, England	Single *	29	M	Prescript Amph	Visual H, Auditory H, Hostility	< 1 week
Wang, 2014, China	1 *	25	M	Meth	Persecutory D, Jealous, Auditory H, Hostility, Social Withdrawal, Flat Affect	1-4 weeks
	2 *	30	M	Meth	Persecutory D, Auditory H, Hostility, NO Disorientation	1-4 weeks
Yeh, 2014, Taiwan	Single	26	M	Amph	Somatic D, Tactile H	1-4 weeks
Young, 1961, USA	Single *	12	M	Prescript Amph	Persecutory D, Somatic D, Visual H, Disorganised Behaviour, Conceptual Disorganisation, Self Harm, Hyperactivity, Inappropriate Affect, Disorientation, Reduced Movement, Poverty of Speech	1-4 weeks
Zeidman, 1975, USA	Single *	44	M	Prescript Amph	Persecutory D, Auditory H, Visual H, Hostility, Religious	*NR*

Note. *NR* = Not reported or unclear; H = hallucinations; D = delusions; * = participants recruited from hospital inpatient/outpatient samples; + = participants recruited from treatment centres; recruitment method not reported or unclear where blank; ~ = participants recruited from private clinics;. 1. Symptoms explicitly noted as absent are denoted with "NO symptom". Amph= Amphetamine. Meth = Methamphetamine. Prescript Amph = Prescription Amphetamines (for example, dextroamphetamine or d-amphetamine). The terms 'amphetamine' and 'methamphetamine' (and the associated street names) have been used interchangeably or inconsistently, and may not reflect forensically verified differences in chemical structure.

Supplementary Tables for Study Two

The relationship between illicit amphetamine use and psychiatric symptom profiles in schizophrenia and affective psychoses

Supplementary Table 1.

Frequency of amphetamine use in past-year group

	Schizophrenia (n=113)	Affective Psychoses (n=92)	Total (n=205)
Less than monthly	60.2 (68)	54.3 (50)	57.6 (118)
1-3 times per month	20.3 (23)	17.4 (16)	19.0 (39)
1-2 days per week	11.5 (13)	18.5 (17)	14.6 (30)
Daily/almost daily	8.0 (9)	9.8 (9)	8.8 (18)

Supplementary Table 2

Table comparing demographics between past-year and former in SZ

	Former amphetamine use		Past-year amphetamine use	
	Schizophrenia	Affective psychoses	Schizophrenia	Affective psychoses
Age in years, M (SD) *	33.9 (0.57)	36.4 (0.65)	31.4 (0.68)	34.3 (0.90)
Male sex, % (n)	76.9 (180)	52.3 (105)	80.5 (91)	57.6 (53)
Age (years) when left school, M (SD)	15.9 (0.11)	16.3 (0.37)	15.9 (0.13)	16.0 (0.15)
Single, never married % (n)	27.3 (64)	40.1 (79)	20.3 (23)	42.4 (39)
Paid employment in past 12 months, % (n)*	31.2 (73)	30.5 (60)	41.6 (47)	41.3 (38)
Duration of illness in years, M (SD) *	12.5 (0.61)	15.2 (0.69)	9.7 (0.69)	13.6 (0.91)
Course of illness, % (n)				
Single episode with recovery	8.6 (20)	3.6 (7)	7.1 (8)	3.3 (3)
Multiple episode with recovery	61.1 (143)	72.6 (143)	55.7 (63)	66.3 (61)
Continuous chronic illness	30.3 (71)	23.9 (47)	37.2 (42)	30.4 (28)
Substance use in past 12 months, % (n)				
Antipsychotics *	90.2 (211)	78.2 (154)	88.5 (100)	77.2 (71)
Mood stabilizers *	17.5 (41)	34.5 (68)	14.1 (16)	39 (36)
Antidepressants	24.4 (57)	44.67 (88)	26.6 (30)	29.3 (27)
Frequent[1] alcohol use *	51.3 (12)	45.7 (90)	62.3 (76)	59.8 (55)
Frequent[1] cannabis use *	30.1 (69)	38.1 (74)	65.8 (73)	61.8 (55)
Other illicit substances *	11.5 (27)	16.2 (32)	46.9 (53)	59.8 (55)
Lifetime cannabis abuse/dependence *	85 (199)	74.6 (147)	91 (103)	82.6 (76)

Note. * = Adjusted for in subsequent regression analyses.

Supplementary Table 3

Prescription medications used in past 12 months

	Former amphetamine use		Past-year amphetamine use	
	Schizophrenia (n=234)	Affective psychoses (n=197)	Schizophrenia (n=113)	Affective psychoses (n=92)
Any medication	96.6 (226)	96.9 (191)	93.8 (106)	90.2 (83)
Antipsychotics	90.2 (211)	78.2 (154)	88.5 (100)	77.2 (71)
Typical - oral	5.1 (12)	4.0 (8)	4.4 (5)	4.3 (4)
Typical - depot	19.7 (46)	14.7 (29)	10.6 (12)	10.9 (10)
Atypical - oral	73.5 (172)	57.4 (113)	73.4 (83)	57.6 (53)
Atypical - depot	14.1 (33)	14.2 (28)	17.7 (20)	14.1 (13)
Atypical - clozapine	22.2 (52)	9.6 (19)	12.4 (14)	5.4 (5)
Mood stabilisers	17.6 (41)	34.6 (68)	14.2 (16)	39.1 (36)
Anxiolytics / Sedatives	17.9 (42)	25.9 (51)	17.7 (20)	26.1 (24)
Antidepressants	24.4 (57)	44.7 (88)	26.6 (30)	29.3 (27)

Supplementary table 4
Unadjusted Univariate Values for Psychiatric Symptoms

Symptom	Schizophrenia			Affective Psychoses		
	OR	95% CI	*P* value	OR	95% CI	*P* value
Hallucinations						
Multiple voices	1.78	1.09 – 2.91	0.021	1.33	0.718 – 2.47	0.364
Running commentary	1.19	0.727 – 1.96	0.484	1.48	0.848 – 2.60	0.166
Non-verbal sounds	1.54	0.941 – 2.51	0.086	.832	0.469 – 1.47	0.529
Any hallucination	2.09	1.25 – 3.48	0.005 *	1.19	0.722 – 1.96	0.493
Delusions						
Persecutory	2.10	1.31 – 3.36	0.002 *	1.19	0.730 – 1.96	0.473
Control	1.19	0.639 – 2.23	0.576	.922	0.419 – 2.02	0.841
Reference	1.41	0.897 – 2.23	0.135	1.34	0.793 – 2.26	0.274
Grandiosity	1.14	0.704 – 1.84	0.593	1.31	0.765 – 2.26	0.319
Bizarre	.990	0.567 – 1.72	0.973	.986	0.473 – 2.05	0.971
Any delusion	1.82	1.08 – 3.07	0.023	1.59	0.942 – 2.70	0.082
Affective symptoms						
Dysphoria	1.94	1.22 – 3.09	0.005 *	1.37	0.787 – 2.41	0.262
Suicidal ideation	1.67	1.01 – 2.77	0.044	1.37	0.883 – 2.25	0.214
Anhedonia	1.92	1.21 – 3.06	0.006 *	1.28	0.745 – 2.22	0.363
Anxiety	.812	0.514 – 1.28	0.373	1.48	0.886 – 2.49	0.133
Elevated mood	2.19	0.954 – 5.06	0.064	1.45	0.879 - 2.42	0.143
Any affective symptom	1.25	0.772 – 2.03	0.360	2.08	0.823 – 5.26	0.121
Disorganised symptoms						
Thoughts racing	2.58	1.26 – 5.27	0.009 *	1.59	0.963 – 2.62	0.069
Distractibility	2.76	1.33 – 5.71	0.006 *	1.49	0.904 – 2.45	0.117
Inappropriate social behaviour	2.97	1.21 – 7.27	0.017	1.89	1.11 – 3.20	0.018
Reckless activity	1.75	0.705 – 4.36	0.227	1.65	0.985 – 2.79	0.057
Any disorganised symptom	1.49	0.92 – 2.42	0.104	1.81	1.01 – 2.99	0.021

1. Asterisks (*) indicate statistically significant difference (p=<0.01).

Supplementary Tables for Study Three

Is there a discrete negative symptom dimension in people who use methamphetamine?

Supplementary Table 1

Factor analysis indices of model fit

	AIC	BIC
One Factor	7755	7882
Two Factors	7550	7737
Three Factors	7466 *	7712 *
Four Factors	7467	7767
Five Factors	7477	7828

Note. * = Lowest (optimal) value. AIC = Akaike Information Criterion; BIC = Bayesian Information Criterion.

Supplementary Table 2

Inter-item correlations for items in positive-activation symptom factor

Item, *r* (p-value)	Grandiosity	UTC	Hallucinations	Tension	Hyperactivity	Excitement	Concept.	Mannerisms	Distractibility
Grandiosity	-	-	-	-	-	-	-	-	-
UTC	0.47 (<.001)	-	-	-	-	-	-	-	-
Hallucinations	0.21 (.008)	0.53 (<.001)	-	-	-	-	-	-	-
Tension	0.10 (.198)	0.21 (.009)	0.25 (.002)	-	-	-	-	-	-
Hyperactivity	0.23 (.003)	0.25 (.002)	0.25 (.002)	0.64 (<.001)	-	-	-	-	-
Excitement	0.30 (<.001)	0.26 (.001)	0.08 (.320)	0.58 (<.001)	0.63 (<.001)	-	-	-	-
Concept. dis.	0.39 (<.001)	0.44 (<.001)	0.11 (.157)	0.42 (<.001)	0.38 (<.001)	0.50 (<.001)	-	-	-
Mannerisms	0.23 (.004)	0.18 (.022)	0.14 (.075)	0.38 (<.001)	0.32 (<.001)	0.21 (.008)	0.17 (.033)	-	-
Distractibility	0.19 (.018)	0.27 (.001)	0.29 (<.001)	0.36 (<.001)	0.28 (<.001)	0.23 (.004)	0.30 (<.001)	0.22 (.007)	
Suspiciousness	0.42 (<.001)	0.61 (<.001)	0.37 (<.001)	0.02 (.833)	0.09 (.258)	0.12 (.124)	0.22 (.005)	0.11 (.163)	0.19 (.018)

Supplementary Table 3

Inter-item correlations for items in affective symptom factor

Item, *r* (p-value)	Depression	Anxiety	Suicidality	Guilt	Hostility
Depression	-	-	-	-	-
Anxiety	0.54 (<.001)	-	-	-	-
Suicidality	0.60 (<.001)	0.44 (<.001)	-	-	-
Guilt	0.45 (<.001)	0.33 (<.001)	0.30 (<.001)	-	-
Hostility	0.15 (.061)	0.39 (<.001)	0.33 (<.001)	0.17 (.041)	-
Somatic Concern	0.20 (.015)	0.18 (.027)	0.16 (.048)	0.29 (<.001)	0.20 (.015)

Supplementary Table 4

Inter-item correlations for items in negative symptom factor

Item, *r* (p-value)	Blunted affect	Emotion.
Blunted affect	-	-
Emotion.	0.73 (<.001)	-
Motor Retardation	0.53 (<.001)	0.32 (<.001)

Note. Emotion. = Emotional withdrawal

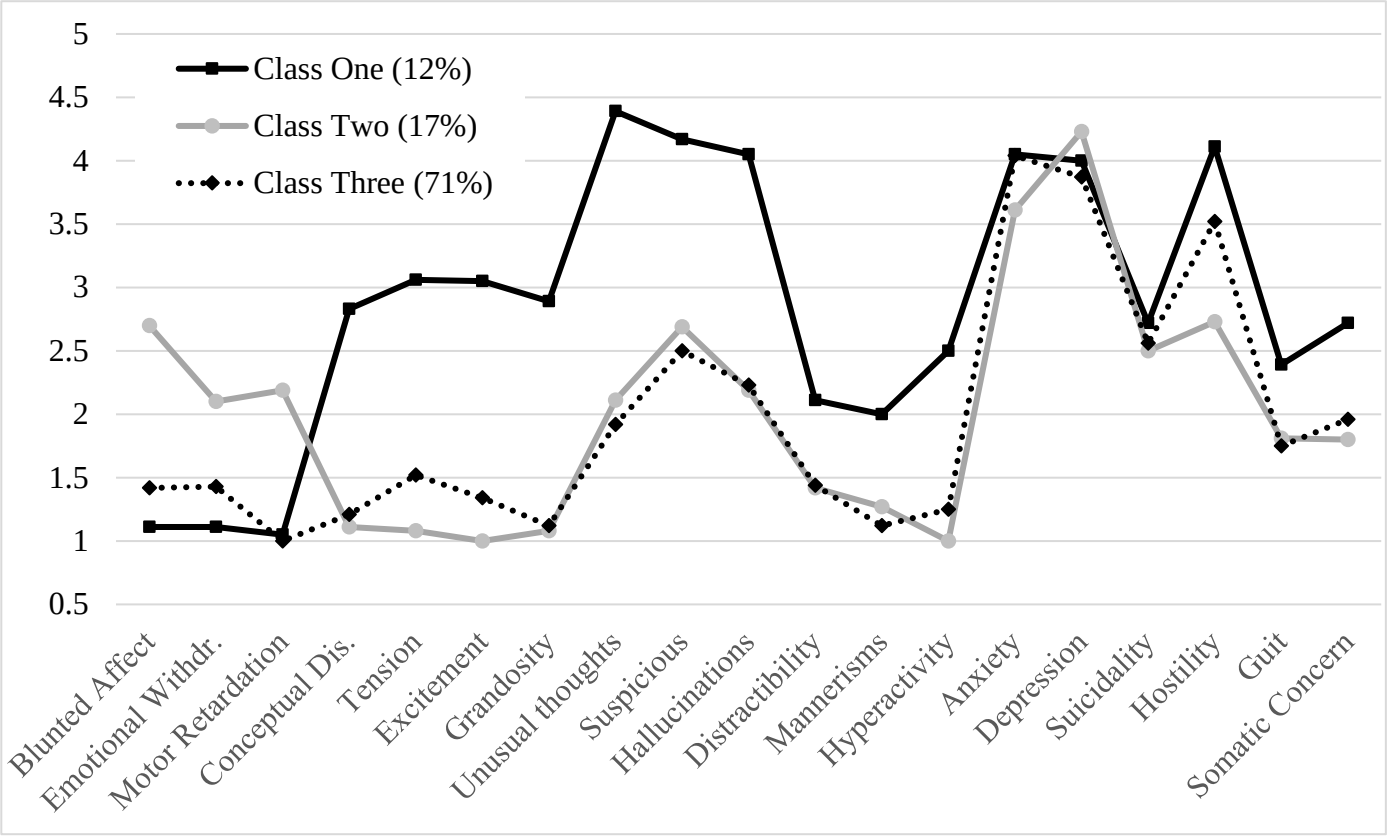
Supplementary Table 5

Comparison of median factor scores by class membership

	Positive Factor	Affective Factor	Negative Factor
Class 1, *Mdn* (*IQR*)	1.45 (0.60 – 2.44)	0.21 (-0.05 – 0.35)	-0.87 (-1.18 – -0.62)
Class 2, *Mdn* (*IQR*)	-1.02 (-2.33 – 0.20)	0.10 (-0.16 – 0.31)	1.35 (1.00 – 2.00)
Class 3, *Mdn* (*IQR*)	-1.52 (-2.48 – -0.73)	-0.24 (-0.56 – -1.13)	-0.43 (-0.60 – -0.01)
	Wilcoxon Rank Sum, z (p-value)		
Class 1 v Class 2	7.50 (<.001)	1.29 (.196)	-9.10 (<.001)
Class 1 v Class 3	8.28 (<.001)	6.33 (<.001)	-5.10 (<.001)
Class 2 v Class 3	0.17 (.167)	4.83 (<.001)	7.85 (<.001)

Supplementary Figure 1

Mean BPRS symptoms by class membership



Note. Unusual Thoughts = Unusual Thought Content; Conceptual Dis. = Conceptual Disorganisation; Hyperactivity = Motor Hyperactivity; Mannerisms = Mannerisms and Posturing;
Emotional Withdr. = Emotional Withdrawal.

Supplementary Table 6

Mean BPRS symptoms by class membership

Class	One	Two	Three	Comparison		
				1 v 2	1 v 3	2 v 3
Anxiety	4.0	3.6	4.0	n/s	n/s	n/s
Depression	4.0	4.2	3.9	n/s	n/s	n/s
Suicidality	2.7	2.5	2.6	*	n/s	n/s
Hostility	4.1	2.7	3.5	n/s	n/s	n/s
Guilt	2.4	1.8	1.7	n/s	*	n/s
Grandiosity	2.9	1.1	1.1	*	*	n/s
Somatic Concerns	2.7	1.8	2.0	n/s	*	n/s
Suspiciousness	4.2	2.7	2.5	*	*	n/s
Unusual Thoughts	4.4	2.1	1.9	*	*	n/s
Hallucinations	4.0	2.2	2.2	*	*	n/s
Conceptual Dis.	2.8	1.1	1.2	*	*	n/s
Tension	3.1	1.1	1.5	*	*	*
Excitement	3.0	1.0	1.3	*	*	*
Distractibility	2.1	1.4	1.4	*	*	n/s
Hyperactivity	2.5	1.0	1.2	*	*	*
Mannerisms	2.0	1.3	1.1	*	*	n/s
Blunted Affect	1.1	2.7	1.4	*	n/s	*
Emotional Withdr.	1.1	2.1	1.4	*	n/s	*
Motor Retardation	1.0	2.2	1.0	*	n/s	*

Note. * p = <.01; n/s = not statistically significant. Class one (n=18, 12%) appears to correspond to the positive-symptom class (in the main text) as these individuals reported significantly higher positive-activation symptoms (suspiciousness, unusual thought content, hallucinations, conceptual disorganisation, tension, excitement, distractibility, hyperactivity, mannerisms) than class one and three. Class two (n=26, 17%) appears to correspond to the negative-symptom class (in the main text) in reporting higher negative symptoms (blunted affect, emotional withdrawal and motor retardation) than class one or two. The largest group, class three (n=109, 71%), corresponds to the low-symptom class in reporting lower positive-activation and negative symptoms than class one or two.

Supplementary Tables for Study Four

Latent psychotic symptom profiles amongst people who use methamphetamine: what do they tell us about existing diagnostic categories?

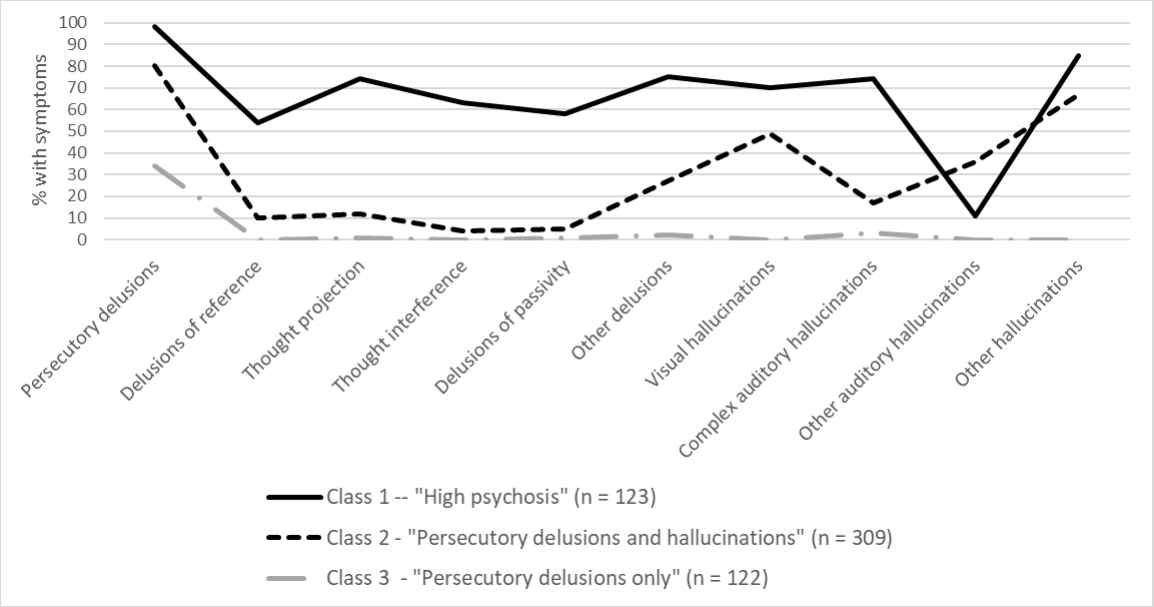
Supplementary Material

CIDI symptoms groupings:

Delusions were grouped as persecutory (beliefs about being spied on, talked about or laughed at, followed or plotted against, or secretly tested), thought projection (hearing other people's thoughts; others hearing their thoughts), thought interference (convinced strange thoughts were being put directly into their mind, or someone could steal their thoughts), passivity (convinced they were under control of a power or force, or felt strange forces working on them, e.g. x-rays or laser beams), reference (believed that they were being sent special messages through television/radio, or a book, newspaper or song was meant only for them), other delusions (erotomania, jealousy, mind reading). Hallucinations were categorized as complex auditory hallucinations (voices commenting on the participant's behavior or discussing the participant; two or more voices talking to each other; the participant having a two-way conversation with voices, voices coming from the participant's body), other auditory hallucinations, visual hallucinations, and other hallucinations (olfactory, gustatory and tactile).

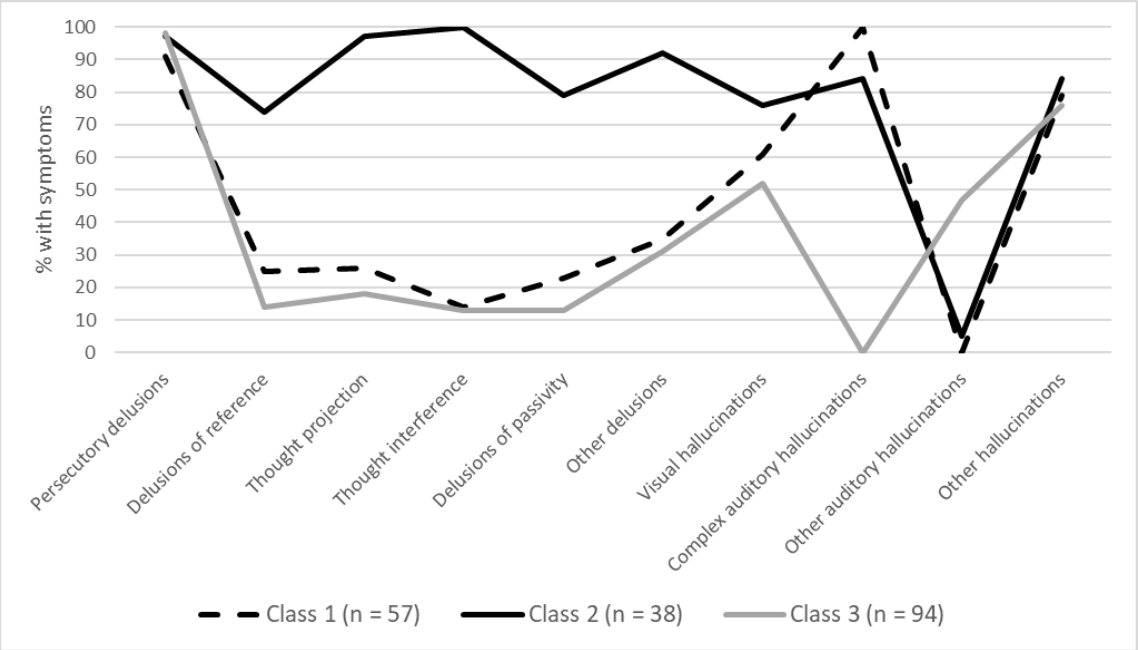
Supplementary Figure 1.

Lifetime symptom prevalence for the three-class models for the full sample.



Supplementary Figure 2.

Lifetime symptom prevalence for the three-class models for participants who met the symptom criteria for schizophrenia.



Supplementary Tables for Study Five

A latent class analysis of psychiatric symptom profiles associated with past-month methamphetamine use

Supplementary Table 1.

Proxy diagnosis of people with methamphetamine-associated psychosis (MAP)

Summary of DSM-IV criteria for MAP[1]	Corresponding item from the CIDI schizophrenia module
A. Prominent delusions or hallucinations.	Individuals presented with either delusions or hallucinations (DSM-IV criteria A1–A2 for SZ)
B. There is evidence that (1) symptoms in Criteria A developed during, or within one month of, methamphetamine intoxication or withdrawal, and (2) methamphetamine use is etiologically related to the disturbance	Symptoms "*always the result of taking medication, drugs or alcohol*" (DSM-IV criteria E for SZ)
C. The disturbance is not better explained by a psychotic disorder that is not substance-induced	Did not meet full DSM-IV diagnostic criteria for schizophrenia based on the full CIDI module
D. The disturbance does not occur exclusively during the course of a delirium	Symptoms were not "*the result of a physical illness or injury*" (DSM-IV criteria E for SZ)
Note. This diagnosis should be made only when symptoms are in excess of those usually associated with the intoxication or withdrawal syndrome and when the symptoms are sufficiently severe to warrant independent clinical attention	Since symptoms begun has participant been less able to do work, or make friends or enjoy social relationships (DSM-IV criteria B for SZ)

1. DSM-IV criteria for MAP are based on the DSM-IV criteria for substance induced psychotic disorder (APA, 1994)
CIDI = Composite International Diagnostic Interview

Supplementary Table 2.

Probability of BPRS-E Symptoms by class membership

Class	One (46%)	Two (29%)	Three (25%)	Total (*n*=160)	Comparison across classes, X^2 (*p*-value) 1 v 2	2 v 3	1 v 3
Anxiety	59	100	56	70	24.9 (<.001)	25.1 (<.001)	0.01 (.755)
Depression	50	100	49	64	33.2 (<.001)	30.8 (<.001)	0.02 (.897)
Suicidality	4	71	33	30	60.6 (<.001)	12.0 (.001)	18.0 (<.001)
Guilt	1	11	8	6	5.6 (.018)	0.2 (.621)	3.1 (.077)
Hostility	36	63	67	52	8.0 (.005)	0.2 (.665)	10.0 (.002)
Somatic concerns	0	9	32	11	6.8 (.009)	7.4 (.007)	27.1 (<.001)
Grandiosity	0	0	32	8	-	17.6 (<.001)	27.1 (<.001)
Unusual thought.	3	22	82	28	11.4 (.001)	31.6 (<.001)	77.7 (<.001)
Suspiciousness	11	46	70	36	18.8 (<.001)	5.2 (.023)	42.1 (<.001)
Hallucinations	4	37	82	33	22.1 (<.001)	18.2 (<.001)	73.9 (<.001)
Self-neglect	30	33	42	34	0.1 (.740)	0.9 (.344)	1.9 (.170)
Conceptual dis.	3	0	20	6	1.3 (.261)	10.1 (.001)	9.7 (.002)
Excitement	3	0	20	6	1.3 (.261)	10.1 (.001)	9.7 (.002)
Distractibility	3	0	15	5	1.3 (.261)	7.4 (.006)	6.0 (.014)
Hyperactivity	0	0	20	5	-	10.1 (.001)	15.9 (<.001)
Tension	0	0	25	6	-	13.0 (<.001)	20.3 (<.001)
Blunted affect	14	0	10	9	6.8 (.009)	4.8 (.028)	0.3 (.585)
Emotional withd.	7	0	2	4	3.2 (.072)	1.2 (.281)	0.9 (.331)

Note. Emotional withd = emotional withdrawal; Conceptual dis. = conceptual disorganisation; Unusual thought = usual thought content (delusional thinking).