MONASH University

Methamphetamine and psychosis: risk and vulnerability factors

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A thesis submitted for the degree of Doctor of Philosophy at Monash University in September 2018

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Contents

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Abstract

This thesis focusses on methamphetamine-associated psychosis (MAP). Methamphetamine is a synthetic stimulant drug and is the most widely used illicit drug worldwide after cannabis. The use of methamphetamine has become a public health concern in many regions, in large part due to the mental health effects of the drug. In Australia, recent estimates suggest that 42.3% of people reporting past year use of the drug were diagnosed with or treated for a mental illness. Psychotic symptoms associated with methamphetamine use form a substantial part of this burden of illness, and contribute to distress and suffering for many individuals and their families.

While it has been established for over 40 years that amphetamine-type substances, like methamphetamine, can trigger psychotic symptoms (1), the phenomenon of methamphetamine-associated psychosis remains poorly understood. Methamphetamine-associated psychosis contributes to a significant burden on acute and mental health services, and considerable distress for individuals and families. Clinicians are often faced with the clinical dilemma of determining whether an individual presenting with methamphetamine-associated psychosis is at risk of developing a more persistent illness, and whether they require ongoing treatment, as a result of considerable uncertainty around risk factors and prognosis for the disorder. Although the syndrome is a widely-studied phenomenon, there remain a number of key gaps in our understanding of its risk factors and correlates, resulting in a lack of clarity in informing a high-risk for psychosis profile in people who use methamphetamine, translating to sub-optimal management and a lack of assertive follow-up of individuals with the disorder.

This thesis comprises of nine chapters that consolidate the contemporary evidence on the risk factors for methamphetamine-associated psychosis, and investigate demographic, clinical and cognitive correlates of the disorder.

Chapter 1 comprises of a manuscript on a clinically-focused overview of MAP and provides background for the topic area of this thesis. Chapter 2 continues with a comprehensive literature review that places MAP within the broader context of the continuum of psychotic experiences, concentrating on the key neurobiological, cognitive and social cognitive correlates of the disorder. Chapter 2 provides an in-depth discussion of the key gaps in the literature and concludes with a background and rationale for the research questions. Chapter 3 is an expanded methodology chapter, describing the overarching structure of the thesis, and the detailed methods, measures and analyses utilised in each individual study.

Chapter 4 investigates demographic correlates of MAP in comparison to primary psychotic disorders through analysis of acute ambulance presentations. Chapter 5 examines clinical correlates of MAP in a group of methamphetamine-dependent individuals seeking specialist outpatient treatment. The study in Chapter 6 is a systematic review of risk factors for methamphetamine-associated psychosis and takes a

rigorous and comprehensive approach to consolidating the literature on existing evidence for correlates of MAP.

Chapters 7-8 then focus on research into cognitive and social cognitive correlates of MAP, in a study of adults presenting with sub-clinical psychotic experiences related to use of the drug. The study in Chapter 7 finds evidence for an association between MAP and facial emotion recognition, but not any other cognitive domains. In addition, we investigated whether particular types of psychotic symptoms are associated with specific emotion recognition deficits. Within Chapter 8, the recognition of discrete emotions is compared between MA users with and without clinically-significant psychotic symptoms, and healthy controls.

Finally, Chapter 9 comprises a discussion that integrates the findings of the thesis, and considers the strengths, limitations, clinical significance and directions for future research on methamphetamine-associated psychosis.

Publications duringenrolment

Arunogiri, S., Gao, C. X., Lloyd, B., Smith, K., & Lubman, D. I. (2015). The role of methamphetamines in psychosis-related ambulance presentations. *Australian & New Zealand Journal of Psychiatry*, *49*(10), 939-946.

Arunogiri, S., Petrie, M., Sharkey, M., & Lubman, D. I. (2017). Key differences in treatment-seeking stimulant users attending a specialised treatment service: a means of early intervention? *Australasian Psychiatry*, *25*(3), 246-249.

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

Arunogiri, S., McKetin, R., Verdejo-Garcia, A., & Lubman, D. I. (2018). The Methamphetamine-Associated Psychosis Spectrum: a Clinically Focused Review. *International Journal of Mental Health and Addiction*, 1-12.

Parts of this thesis were presented at the following conferences and symposiums:

Arunogiri, S., McKetin, R., Verdejo-Garcia, A., Rubenis, A.J., Fitzpatrick, R.E., Lubman, D.I., (2018) *Association between methamphetamine psychosis & facial emotion recognition*. Poster Presentation at College for Problems on Drug Dependence (CPDD) June 2018. San Diego, USA.

Arunogiri, S. (2018) *Methamphetamine & Psychosis: perspectives from research for frontline clinicians.* Invited speaker at NorthWestern Melbourne and Eastern Melbourne Primary Health Networks (PHNs) Alcohol and Other Drug (AOD) Forum, June 2018. Melbourne, Australia.

Arunogiri, S. (2018) *Methamphetamine associated psychosis: unpacking the links and understanding how best to help*. Invited presentation for Connect & Learn Webinar Series, online, May 2018.

Arunogiri, S. (2018) *Methamphetamine psychosis*. Invited presentation, Forensicare Mental Health Services, May 2018. Melbourne, Australia.

Arunogiri, S. (2018) *It's a drug and alcohol problem, not a mental health problem.* Symposium at Royal Australian and New Zealand College of Psychiatrists (RANZCP) Congress, May 2018. Auckland, New Zealand.

Arunogiri, S. (2017) *Methamphetamine psychosis.* Invited speaker at Royal Australian and New Zealand College of Psychiatrists (RANZCP) Western Australia (WA) Branch of Sociocultural Psychiatry Seminar, October 2017. Perth, WesternAustralia.

Arunogiri, S. (2017) *Systematic Review of Risk Factors for Methamphetamine Associated Psychosis*. Speaker at Symposium on Methamphetamine Associated Psychosis. International Federation of Psychiatric Epidemiology (IFPE) Conference 2017. Melbourne, Australia.

Arunogiri, S. (2017) *Methamphetamine psychosis: integrated approaches to treatment*. Invited speaker at Royal Australian and New Zealand College of Psychiatrists (RANZCP) Queensland Branch Conference. Noosa, Queensland.

Arunogiri, S. (2017) *Methamphetamine use and psychosis: approaches to assessment and treatment.* Invited speaker, Northern Area Mental Health Services, February 2017. Melbourne, Australia.

Thesis including published works declaration

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes two reviews and five original papers submitted or published in peer reviewed journals. The core theme of the thesis relates to predictors and correlates of methamphetamine psychosis. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the student, working within Eastern Health Clinical School under the supervision of Prof Dan Lubman, A/Prof Antonio Verdejo-Garcia and A/Prof Rebecca McKetin.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of *Chapters 1, 4, 5, 6 and 8* my contribution to the work involved the following:

Thesis Chapter	Publication Title	Status *(published, in press, accepted or returned for revision)*	Nature and % of student contribution	Co-author name(s) Nature and % of Co-author's contribution*	Co-author(s), Monash student Y/N*
1	The Methamphetamine-Associated Psychosis Spectrum: A Clinically Focused Review	Published	70% Concept, review and synthesis of literature, manuscript preparation	1) Rebecca McKetin, review of manuscript 10% 2) Antonio Verdejo-Garcia, review of manuscript 10% 3) Dan Lubman, review of manuscript 10%	No
4	The role of methamphetamines in psychosis-related ambulance presentations	Published	60% Concept, manuscript preparation	1) Caroline Gao, statistical analysis 25% 2) Belinda Lloyd guidance on analysis and dataset 5% 3) Karen Smith guidance on analysis and access to data 5% 4) Dan Lubman review of manuscript 5%	No
5	Key differences in treatment-seeking stimulant users attending a specialised treatment service: a means of early intervention	Published	70% Concept, data collection, manuscript preparation	1) Margret Petrie data collection, 10% 2) Michelle Sharkey data collection, 10% 3) Dan Lubman review of manuscript 10%	No
6	A systematic review of risk factors for methamphetamine-	Published	70% Concept, review protocol,	1) James Foulds search, data extraction	No

	associated psychosis		search and data extraction, manuscript preparation	15% 2) Rebecca McKetin guidance on data extraction, review of manuscript 10% 3) Dan Lubman review of manuscript 5%	
8	Methamphetamine use, psychotic symptoms and emotion recognition	Under Preparation*	70% Concept, data collection, data analysis, manuscript preparation	1) Rebecca McKetin, manuscript review 5% 2) Antonio Verdejo-Garcia, manuscript review 5% 3) Adam Rubenis, data collection 7.5% 4) Rebecca Fitzpatrick, data collection 7.5% 5) Dan Lubman, review of manuscript 5%	Co-authors 3-4 Yes

*The paper in Chapter 8 is currently under preparation for resubmission.

I have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student signature: [redacted] **Date:** 14/02/19

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor signature: [redacted] **Date:** 14/02/19

Acknowledgements

My candidature was supported by an Australian Postgraduate Award (APA), and subsequently a National Health and Medical Research Council (NHMRC) Postgraduate Scholarship (Grant Number: 1093778). This research was also supported by a Royal Australian and New Zealand College of Psychiatrists (RANZCP) Research and Education Foundation Grant, and the 2016 Windermere Foundation Syd Allen Doctoral Scholarship in Health-Medicine.

Firstly, I would like to acknowledge the generosity of the research participants and staff who contributed to the work in this thesis. In addition, I am truly grateful for the substantial efforts of my co-students Adam Rubenis and Rebecca Fitzpatrick for their assistance with data collection on this thesis.

The stories and journeys of my patients and families informed the research in this thesis, and I hope that the work contained here goes some way towards developing a means to alleviate their suffering.

I owe a debt of gratitude to my supervision team. To Dan for his pragmatism, sound judgement, sense of humour and persistent faith in me in this, and other, efforts. To Antonio for his calm and considered perspective. And to Rebecca, for her attention to detail, her clarity of thought, and always, her kindness.

And finally, I am thankful for the people who have made this thesis worthwhile, and without whom it would never have manifested. My mother, for always being there when I needed her. And to my son Julian and my husband Surain, for grounding me and reminding me of what is important in life.

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Glossary

The following abbreviations are defined the first time they appear in the text.

MA	Methamphetamine
MD	Methamphetamine dependence
MAP	Methamphetamine-associated psychosis
SIPD	Substance-induced psychotic disorder
FER	Facial emotion recognition
EFT	Ekman Faces Test
HVLT	Hopkin's Verbal Memory Test
IGT	Iowa Gambling Task
DDT	Delay DiscountingTask
BPRS	Brief Psychiatric Rating Scale

Chapter 1 Background

1.1 PREAMBLE

This chapter constitutes a manuscript which provides an overview of the central theme of this thesis and a background to this research area.

Declaration for Thesis Chapter 1

Monash University

Declaration by candidate

In the case of Chapter 1, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation, review and synthesis of literature, manuscript preparation	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution
A/Prof Rebecca McKetin	Review of manuscript
A/Prof Antonio Verdejo-Garcia	Review of manuscript
Prof Dan Lubman	Supervision and review of manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 02/09/18
Main Supervisor's Signature	[redacted]	**Date** 02/09/18

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Int J Ment Health Addiction
https://doi.org/10.1007/s11469-018-9934-4

ORIGINAL ARTICLE

The Methamphetamine-Associated Psychosis Spectrum: a Clinically Focused Review

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Abstract Methamphetamine use is a global concern, and methamphetamine-associated psychosis (MAP) is a particular harm resulting from regular use of the drug that causes significant distress and burden on health and social services. This paper aims to provide a clinically focussed and up-to-date overview of the prevalence, risk factors, and clinical and cognitive features of MAP. The prevalence of MAP ranges between 15 and 30% in recreational settings and up to 60% in some inpatient treatment settings, with up to a third of people with MAP later diagnosed with persistent psychotic disorders. The frequency of methamphetamine use and severity of dependence are the most consistent risk factors for MAP, but other predictors such as genetic vulnerability, a family history of psychotic illness, or trauma also play a role. People with MAP can vary in their presentation, from brief delusional experiences, to persistent psychosis characterised by first-rank symptoms and cognitive impairment. Contemporary conceptualisations of MAP need to incorporate this spectrum of clinical presentations in order to inform clinical decision-making, service provision, and research directions.

Keywords Methamphetamine · Amphetamine · Psychosis · Substance-induced psychosis · Dual diagnosis · Cognition · Genetics

Illicit methamphetamine (MA) use is a growing public health concern worldwide, with data from the United Nations Office on Drugs and Crime suggesting that seizures of the drug are at a record high, particularly in North America, East and South-East Asia, and

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Published online: 21 May 2018

Oceania (United Nations Office on Drugs and Crime 2016). In Australia, increasing use of the crystalline form of the drug and increasing purity and potency have resulted in a rise in a wide range of physical and psychological harms (Scott et al. 2015). People who use methamphetamine regularly experience high levels of psychological distress and have higher rates of depression and anxiety symptoms (McKetin et al. 2011; Zweben et al. 2004), while methamphetamine-associated psychosis (MAP) contributes a substantial proportion of health service utilisation resulting from MA use (McKetin et al. 2017a). While regular use of the drug is commonly associated with psychotic symptoms, the underlying mechanisms by which this occurs, and the risk factors, correlates and trajectory of the syndrome are poorly understood. Further, while there are several similarities between MAP and primary psychotic disorders, it remains unclear how the two are related. This review will provide an up-to-date overview of what is known about MAP and offer a clinically focussed characterisation of the phenomenon that will assist practitioners in their assessment and management of patients.

The Prevalence of Methamphetamine-Associated Psychosis

A range of psychotic phenomena have been reported in association with MA use, from transient states during periods of intoxication to more persistent syndromes that resemble schizophreniform disorder (Rebecca McKetin, Baker, Dawe, Voce, & Lubman, 2017a; McKetin et al. b). The term methamphetamine-associated psychosis (MAP) has been proposed by some authors to refer to the full spectrum of psychotic symptoms that can occur in methamphetamine users (Mathias et al. 2008). Amphetamine-type stimulants are known to be psychotogenic. For example, psychotic symptoms are cited as adverse effects of prescription stimulant medications (Ross 2006). In experimental situations, increasing doses of amphetamine and MA have been demonstrated to trigger psychotic symptoms in healthy controls in a dose-dependent manner (Angrist and Gershon 1970; D. S. Bell 1973; McKetin 2018). Despite this evidence, the relationship between psychosis and MA use remains poorly understood. In both experimental and observational studies, there is a subset of individuals who do not appear to develop psychotic symptoms despite high-dose methamphetamine use. Conversely, there are individuals who can develop psychosis following very limited exposure to the drug. Thus, methamphetamine use alone may not be sufficient to trigger psychosis.

The prevalence of the phenomenon appears to vary widely, from 15 to 23% in recreational or community settings (McKetin et al. 2010; McKetin et al. 2006) to 60% in dependent users within treatment settings (Ding et al. 2014; McKetin et al. 2013; Sulaiman et al. 2014). Across studies, there can be differing definitions of methamphetamine-associated psychosis, with some measuring a diagnosis of clinical disorder and others assessing recent psychosis-like experiences (Grant et al. 2012). Many more individuals present with sub-threshold psychotic symptoms that do not meet criteria for a diagnosis of a disorder, so studies utilising trans-diagnostic or dimensional assessment tools often have higher estimates of prevalence. Even when only clinical disorders are considered, there can still be some variability in prevalence, and this may relate to a number of underlying factors that contribute to the risk of psychotic symptoms.

Risk Factors for Methamphetamine-Associated Psychosis

A recent systematic review of risk factors for MAP found that people who used MA more frequently, or who had a diagnosis of MA dependence, were most likely to experience psychotic symptoms (Arunogiri et al. 2018). Both polydrug use and dependence have also been shown to increase the risk of MAP. While there is consistent evidence that sociodemographic factors, such as age, gender, or years of education, do not predict the likelihood of psychosis, the role of a range of other environmental factors remains unclear. For instance, Chen and colleagues were the first to find a link between MAP and a family history of psychosis and estimated that people with a lifetime history of a MA-induced psychotic disorder had about five times higher familial loading for schizophrenia (Chen et al. 2005). More recent studies have replicated this finding, suggesting a family history of psychotic disorder, whether schizophrenia or bipolar disorder, is more common in people with MAP, particularly persistent types of MAP (Hides et al. 2015; McKetin et al. 2017a, b). A history of childhood trauma is common in people with MA dependence, and one study identified that people with three or more types of adverse childhood experiences had 4.5 times higher odds of reporting a lifetime MA-induced psychotic disorder (Ding et al. 2014). Premorbid schizoid or schizotypal personality traits have also been found to be more common in people who experience MAP. Importantly, these are all factors that have been shown to be associated with risk for developing schizophrenia (van Os et al. 2010), giving rise to the possibility of a shared aetiological pathway for MAP and schizophrenia.

Studies that have explored the role of genetic vulnerability in the phenomenon of MAP have found that some of the genetic polymorphisms associated with MAP are also implicated in schizophrenia and in the risk of the development of other drug use disorders. For instance, DTNBP1 is one of the most promising candidate genes for schizophrenia, and one Japanese study has identified variation in this gene to be associated with MAP (Kishimoto et al. 2008). It is thought to have a role in dopamine and glutamate signalling pathways (Papaleo et al. 2012) and impacts on cognition (Zhang et al. 2010). Other genes that have a role in dopamine system function, such as SNCA (alpha synuclein) or CLN3 and FBP1, have also been implicated in both MAP and schizophrenia (Breen et al. 2016). This has potential implications for conceptualising the phenomenon of MAP, given that dysregulation of the dopamine and glutamate neurotransmitter systems is understood to be critical in the development of primary psychotic disorders such as schizophrenia (Howes et al. 2015; Paparelli et al. 2011). However, research is still required into how these genetic vulnerabilities may relate to environmental stressors, exposure to MA and to other drugs, and to primary psychotic disorders.

In addition, there is evidence that sensitisation may occur in MAP and that each experience of psychotic symptoms may increase vulnerability to further episodes with continued exposure to MA (Curran et al. 2004). It is proposed that this phenomenon may be underpinned by dysregulation of the dopamine system and the neuroadaptation that occurs following prolonged exposure to MA.

Transition to a Primary Psychotic Disorder Diagnosis

A key dilemma for many clinicians working in this area is how to distinguish which individuals who experience acute psychotic symptoms are likely to develop persistent

symptoms or transition to a diagnosis of a primary psychotic disorder. Current diagnostic manuals, such as the DSM-5, define persistence as symptoms that continue for more than a month or more following the period of substance intoxication or cessation (American Psychiatric Association 2013). Indeed, the proportion of people with an initial acute methamphetamine-associated psychotic episode who are later diagnosed with a primary psychotic disorder, such as schizophrenia or bipolar disorder, is high, with estimates across studies in the range of 19–33% (see Table 1). In addition, one study estimated that people with methamphetamine-related disorders had a ninefold increase in the risk of developing schizophrenia in comparison to the general population (Callaghan et al. 2012). However, these estimates have generally been derived from population-based linkage studies, examining rates of admission to hospital for psychotic disorders, rather than direct prospective follow-up of methamphetamine-using cohorts. This raises the possibility that those identified within the persistent disorder group include people with a primary psychotic disorder who were initially misdiagnosed as MAP. It also does not capture individuals who are later diagnosed with a persistent disorder but are not admitted to hospital, and so may be an underestimate of the true rate of conversion. Regardless, this research demonstrates that a substantial proportion of people who have MAP later develop persistent psychoses, highlighting the importance of identifying key phenotypes that may predict which individuals are likely to develop a persistent form of psychosis.

Table 1 Transition to primary psychotic disorder in people with stimulant-associated psychosis

Study, date	*n*	Follow-up	Conversion to primary psychotic disorder (%)	Comments
Kittirattanapaiboon et al. 2010[a]	449	7 years	22	• Thailand • Prospective cohort following methamphetamine-induced psychosis hospital admission
Medhus et al. 2015[b]	12	6 years	33	• Norway • Prospective cohort following amphetamine-induced psychosis hospital admission • Small sample, large proportion of initial sample lost to follow-up
Niemi-Pynttäri et al. 2013[c]	825	8 years	30	• Finland • Population based longitudinal cohort; hospital discharge register
Alderson et al. 2017[d]	273	15.5 years	19.1	• Scotland • Population-based longitudinal cohort based on hospital records
Starzer et al. 2017[e]	555	20 years	32.3	• Denmark • Population-based longitudinal cohort based on linkage of inpatient and outpatient records

[a] Kittirattanapaiboon et al. (2010)

[b] Medhus et al. (2015)

[c] Niemi-Pynttäri et al. (2013)

[d] Alderson et al. (2017)

[e] Starzer et al. (2017)

Phenomenology of MAP

Initial studies of people with MAP suggested that positive symptoms were a hallmark of the disorder and that negative symptoms were rarely observed (Bell 1965; Janowsky and Risch 1979; Sato et al. 1992). In fact, psychotic symptoms in the context of intoxication with methamphetamine were initially considered indistinguishable from an acute psychosis related to schizophrenia (Srisurapanont et al. 2011), with auditory hallucinations and suspicious or paranoid delusions found to be the most common feature of both presentations (Srisurapanont et al. 2003; Srisurapanont et al. 2011). Visual and tactile hallucinations and particularly formication, the sensation of insects crawling under the skin, are reported to be more common in MAP in comparison to other types of psychoses (Wang et al. 2016).

More recent studies examining the phenomenology of MAP have highlighted that there may be variations in presentation that correlate with sub-types and severity of the disorder. For instance, one study of 40 community-based methamphetamine-dependent participants with a lifetime history of subclinical MAP found three different types of psychotic symptom profiles (Bousman et al. 2014). The authors identified that while delusions occur in most people with MAP, only some appear to have hallucinations. The study also measured a subset of Schneiderian first-rank symptoms, delusions of control or passivity of thought, and found that a minority of participants presented with such symptoms, as well as other types of hallucinations and delusions. In contrast, another study in a hospitalised sample of participants with MAP found that delusions of thought broadcasting were more common in schizophrenia, while auditory hallucinations of voice conversing were more common in MAP; but overall, there was no significant difference between the MAP and schizophrenia groups for any other first-rank symptoms (Shelly et al. 2016).

Several studies have suggested that there are distinct symptom profiles for brief and transient MAP compared to persistent MAP (Chen et al. 2015; Hides et al. 2015; McKetin et al. 2016a; McKetin et al. 2017a, b). The presence of negative symptoms or first-rank symptoms may correlate with a more persistent type of psychosis that resembles primary psychotic disorders, such as schizophrenia or bipolar disorder (Chen et al. 2015; Hides et al. 2015; McKetin et al. 2017a).

Cognition

Individuals with long-term methamphetamine use have been found to present with impairments in episodic memory, executive functioning, and psycho-motor functioning, with medium effect sizes found across these domains in meta-analyses (Scott et al. 2007). These impairments have been proposed to arise from methamphetamine-related neurotoxicity in dopaminergic and serotonergic fronto-striatal and limbic circuits (Panenka et al. 2013; Scott et al. 2007). Neuroimaging studies also support changes in dopamine neurotransmission in these areas (Ashok et al. 2017; Sekine et al. 2001; Sekine et al. 2003). A number of studies of executive functioning have highlighted the association of impulsivity and impaired decision-making in increasing susceptibility to relapse (Gowin et al. 2014; Paulus et al. 2005; J. C. Scott et al. 2007), to risk-taking behaviours, or to poorer psychosocial outcomes (Scott et al. 2007). It remains unclear how these deficits relate to methamphetamine use patterns or doses (Dean et al. 2013) or to other comorbidities that can impact on cognitive function, such as psychiatric disorders or other substance use disorders.

A few recent studies have suggested that methamphetamine-dependent individuals with MAP have particular neurocognitive impairments that differ from individuals with methamphetamine dependence without psychosis (Chen et al. 2015; Ezzatpanah et al. 2014; Jacobs et al. 2008) (Table 2). This is marked by greater impairment of verbal memory, verbal fluency, attention, processing speed, and executive function, compared both with healthy controls and also with individuals with methamphetamine dependence but no psychotic symptoms or only brief psychotic symptoms (Chen et al. 2015). Furthermore, individuals with persistent MAP appear to have a cognitive profile that resembles individuals with chronic schizophrenia. Cognition has been long been considered as a core symptom domain in schizophrenia, and research in this area suggests that both cognitive deficits and psychotic symptoms may potentially be conceptualised as phenotypes of common neurobiological dysfunction (Garety et al. 2007; Smith et al. 2009).

The MAP Spectrum and How It Relates to Primary Psychotic Disorders

Multiple similarities may potentially exist between MAP and primary psychotic disorders, including shared genetic vulnerabilities, environmental risk factors, and clinical and cognitive phenotypes. This has implications for our understanding of MAP, suggesting a continuity between MAP and primary psychotic disorders (Bramness and Rognli 2016; Paparelli et al. 2011; Rognli and Bramness 2015). However, much of the research in this area has been cross-sectional in nature, precluding the ability to draw causal inferences. In the absence of data from large prospective cohort studies, we raise the potential of the following framework that draws on the existing evidence, in order to assist clinical decision-making on the assessment and management of MAP. In a recent review, Bramness and colleagues extended the traditional stress-vulnerability paradigm of schizophrenia to the conceptualisation of MAP, describing methamphetamine use as a stress that interacts with underlying genetic and environmental vulnerability factors, towards the development of a primary psychotic disorder (Bramness and Rognli 2016) While this model helps structure our understanding of the underpinnings of MAP, it does not inform the clinical assessment of the phenomenon or its presenting features. The evidence reviewed in this paper therefore adds to this model by providing a range of phenotypes, adding greater detail to the characterisation of MAP, and providing domains for further investigation as markers of vulnerability (see Fig. 1).

In summary, while many people who use methamphetamine experience transient psychotic symptoms, a subset of individuals appear to have lasting symptoms that persist beyond the period of intoxication (e.g. fora number of days to weeks). A further subset of people develop more prolonged symptoms that may persist for weeks to months following cessation of the drug, which then may be considered to be consistent with a primary psychotic disorder such as schizophrenia or bipolar disorder. Both the nature and duration of these psychotic symptoms is thus highly variable. At one end of the spectrum, individuals report brief experiences of positive symptoms, such as suspiciousness and hallucinations. The persistent syndrome at the other end of the spectrum is characterised by negative symptoms and more marked cognitive impairment that resembles schizophrenia. Within this framework, people with acute MAP may present with brief and limited psychotic symptoms characterised by persecutory delusions, but without executive cognitive impairment or first-rank symptoms. Conversely, individuals presenting with persistent MAP would be more likely to present with the following features—first-rank symptoms, negative symptoms, and cognitive impairment.

Table 2 Studies of cognition in methamphetamine psychosis

Study (date)	MAP, *n*	Comparison group, *n*	Duration of abstinence	Cognitive domains assessed	Outcomes	Comments
(Jacobs et al. 2008)	20	Paranoid SCZ (19)	Not reported; current use prior to inpatient admission	Attention/concentration, learning, memory, executive functioning, motor, verbal, SIP	• No significant differences between groups on any domain • Both groups presented with impairment consistent with that expected for schizophrenia	• Small sample • Participants with any other substance dependence excluded • All participants were receiving antipsychotic medication
(Bouchard et al. 2013)	*N* = 172 methamphetamine psychosis		Current use	Attention/concentration, learning, memory, executive functioning, decision-making	• Two distinct clusters of participants, suggesting that poorer performance on decision-making, learning, and memory tasks correlated with slightly more negative symptoms	• Did not exclude individuals with a history of psychiatric disorder (16.6% schizophrenia spectrum, 8.2% bipolar disorder, 21.2% depression)
(Ezzatpanah et al. 2014)	30	SCZ (30), healthy controls (30)	Not reported; current use prior to inpatient admission	Attention (selective, sustained), memory, executive functioning (Wisconsin Card Sorting, Stroop, VSAT, Wechsler memory)	• Healthy controls performed better than both MAP and SCZ groups in all domains • No significant differences between MAP and SCZ groups in all domains except sustained attention (SCZ poorer performance on VSAT)	• Comparison groups matched on age, gender, and education • MAP and SCZ groups were receiving antipsychotic medication
(Chen et al. 2015)	50 METH + BP*; 50 METH + PP*	25 METH − P*; 67 healthy controls; 54 SCZ	9.8–36.2 weeks	Verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, executive function	• Cognitive function in METH + PP compared with SCZ; and was worse than METH − P	• Comparisons controlled for age, gender, and educations and for antipsychotic medication use

Table 2 (continued)

Study (date)	MAP, *n*	Comparison group, *n*	Duration of abstinence	Cognitive domains assessed	Outcomes	Comments
					• All domains: healthy control and METH − P and METH + BP groups performed better than METH + PP and SCZ groups • Negative symptoms correlated significantly w all cognitive domains; positive symptoms did not correlate with any domain	

MAP, methamphetamine-associated psychosis; *SCZ*, schizophrenia; *SIP*, speed of information processing

*METH + BP: brief psychosis: symptoms that disappeared < 1 month after ceasing MA use; persistent psychosis: symptoms that disappeared > 1 month after ceasing MA use; METH − P: MA use and no psychosis

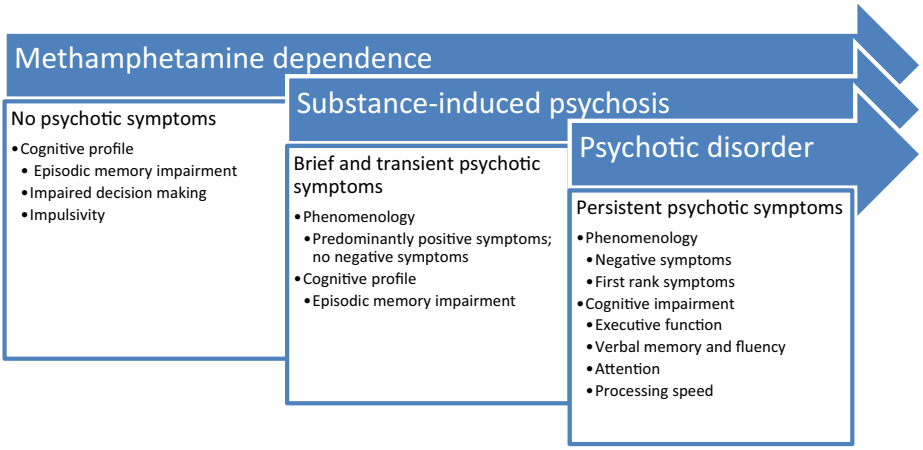

Fig. 1 MAP spectrum

Although based on preliminary evidence, this conceptualisation has a number of implications. Clinically, it can potentially help practitioners characterise and classify presentations of MAP. From a systems perspective, this model raises the opportunity of treating MAP within the context of mental health paradigms for early psychosis, rather than purely within the context of alcohol and other drug treatment provisions. Finally, this framework can help inform directions for future research into the validity of phenotypes for MAP, including the characterisation of negative symptoms, and the specific neurocognitive profiles that reflect vulnerability or resilience. This will assist in building a better informed high-risk model for persistent psychosis in individuals who use illicit methamphetamines.

Compliance with Ethical Standards

Conflict of Interest Authors RM and AVG declare that they have no conflict of interest. Author SA was supported by an Australian National Health and Medical Research Council (NHMRC) postgraduate scholarship (Grant No. 1093778). Author DL has provided consultancy advice to Lundbeck and Indivior and has received travel support and speaker honoraria from Astra Zeneca, Bristol Myers Squibb, Janssen, Lundbeck, Servier, and Shire.

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1.2 SUMMARY

In summary, the overview presented in this publication has potential relevance for clinicians working with individuals who use methamphetamine regularly, by improving characterisation of the heterogeneous phenotypes of methamphetamine-associated psychosis. The evidence presented in this introductory paper identified a number of promising domains for further research into vulnerability factors, including aspects of phenomenology and cognition.

However, as highlighted in the paper, there are key gaps in the existing literature that inform this preliminary framework, including elucidation of markers of psychosis-proneness in methamphetamine-using cohorts, and clarification of the relationship between cognition and methamphetamine-associated psychotic symptoms.

Therefore, the aim of this thesis is to address these gaps through a range of approaches. The key research questions and hypotheses of the thesis will be introduced in Chapter 2.

Chapter 2

Introduction & Literature Review

Following on from the overview of methamphetamine-associated psychosis presented in Chapter 1, this Chapter provides a more in-depth discussion of the literature on the neurobiological, cognitive and phenomenological correlates of the disorder, and how it fits with models of primary psychosis and 'psychosis proneness'.

The thesis has two sections, (i) focusing firstly on the role of methamphetamine use as a correlate of psychosis, and (ii) secondly, investigating cognitive markers of psychotic symptoms in methamphetamine-using adults. The literature review will be organized by these aims, with each section concluding with an overview of the key gaps, research aims and hypotheses. The terminology used throughout this thesis will be defined in this chapter.

2.1 AN INTRODUCTION TO METHAMPHETAMINE USE, METHAMPHETAMINE USE DISORDER AND PSYCHOSIS SYMPTOMS

2.1.1 THE EPIDEMIOLOGY OF METHAMPHETAMINE USE

Amphetamine-type stimulants (ATS) are the second most commonly used illicit drug class worldwide (2). Amphetamine and methamphetamine have been estimated to contribute to the greatest drug-related burden of disease worldwide after opioids, and recent data reflect the highest seizures of amphetamine-type stimulants to date in Oceania and Asia (3).

In Australia, 1.4% of the population have used MA in the past year, with 20% of these individuals reporting at least weekly use (4). There is growing concern about the problems associated with methamphetamine use in Australia, particularly because of the uptake of the more pure crystalline form of the drug (known colloquially as ice), including amongst people who use the drug regularly (4). The crystalline form has been associated with an increase in the risk of a wide range of psychological and physical harms (5, 6). Recent Australian data suggests that up to 42% of people using methamphetamine regularly have a mental illness (4), and the drug contributes to a significant burden on acute health and psychiatric services, with an estimated 90,800 emergency department presentations and 50,700 psychiatric inpatient admissions annually Australia-wide believed to be attributable to methamphetamine use (7).

2.1.2 AN OVERVIEW OF THE CLINICAL PHARMACOLOGY OF METHAMPHETAMINE

Methamphetamine is a synthetic drug and belongs to a class of stimulants referred to as 'amphetamine-type substances' or 'ATS'. The ATS group includes a range of substances, some

used therapeutically in the treatment of narcolepsy, attention-deficit hyperactivity disorder and obesity (3). Methamphetamine is easily manufactured from readily available precursors, such as pseudoephedrine and ephedrine. Methamphetamine base is a colourless odourless oil and insoluble in water, while the salt, methamphetamine hydrochloride, occurs as white powder or as crystals (8). The powder form is colloquially known as 'speed', whereas the pure crystalline salt is known as "ice" and is the commonest form of illicit methamphetamine used in Australia (4).

Methamphetamine is a structural analogue of amphetamine, with a methyl group. It is a highly lipophilic chemical which facilitates its transfer across the blood-brain barrier (9). The route of administration of methamphetamine impacts on its bioavailability and time to onset of action (8). In Australia, the main routes of use of illicit methamphetamine are via inhalation (smoking), or injection (10). Via an injecting route, methamphetamine typically reaches peak plasma concentration within 6 minutes, and peak subjective effect within 15 minutes; in comparison, while subjective peak effects are reported within 20 minutes with smoking, the peak plasma concentration takes up to 2 ½ hours to be reached (8). The metabolism of methamphetamine is primarily via the cytochrome P450 2D6 liver enzyme system, with metabolites not considered to be clinically active (8). Subjective effects tend to decrease over a period of about four hours. Recreational use usually involves repeated doses of the drug in a short space of time, with typical binge patterns of use described as up to four doses per day, over periods of two to four days (8). When used in this way, the cumulative dose of the drug can rise substantially, resulting in a significantly higher dose than that described in experimental studies, and resulting in detectable urinary levels of methamphetamine for up to a week following use (11).

Methamphetamine and other ATS are structurally very similar to monoamine neurotransmitters, namely dopamine, noradrenaline and 5-hydroxytryptamine (5-HT, serotonin) (8, 9) . Acute administration of methamphetamine results in a substantial increase in synaptic monoamine concentrations in the central nervous system, particularly dopamine and noradrenaline. This increase is mediated by three mechanisms, (i) monoamine release, (ii) competitive monoamine reuptake inhibition and (iii) inhibition of breakdown of monoamines by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT) (9). Acutely, methamphetamine administration results in a substantial increase in the concentration of monoamines in the central nervous system, in the order of 400-1500% of baseline levels of noradrenaline and dopamine, with a fast onset and offset of action (9). In vivo, dose dependent

increases are observed in the extracellular concentration of noradrenaline in the prefrontal cortex and dopamine in the striatum, with additional impact on serotonergic and glutamatergic systems (9, 11). The onset and extent of this effect is also influenced by route of administration, with inhalation (i.e., chasing or smoking the crystalline form of methamphetamine) and intravenous routes of use resulting in much faster delivery of the drug to the central nervous system in comparison to oral ingestion (9). In contrast to acute administration in experimental settings, recreational use or abuse is associated with long-term repeated exposure to high doses of the drug. This pattern of use is thought to result in neurotoxicity, with some evidence of potentially irreversible oxidative damage to nerve terminals in dopaminergic and serotonergic circuits (12-14). Other studies suggest that chronic use results in neuroadaptation, rather than neurotoxicity, in dopaminergic circuitry (15).

2.1.3 METHAMPHETAMINE USE DISORDER

Repeated use of methamphetamine can lead to dose escalation, tolerance, withdrawal, cravings and subsequent dependence. Stimulant dependence (DSM-IV) or use disorder (DSM-5) diagnoses refer to a pattern of use that leads to clinically significant impairment or distress, and broadly encompass domains of impaired control, impairment or impact on social function, continuing use despite evidence of risk, and evidence of tolerance and withdrawal(16). People who use methamphetamine weekly or more are likely to experience at least some symptoms of methamphetamine use disorder (17) with an estimated 160,000 (95% CI, 110,000- 232,000) dependent adult users in Australia (18). Correlates of dependent use include more frequent use and injecting use (19-21). Dependent use is associated with an increased risk of experiencing a range of harms related to the drug, including significant physical and mental health problems requiring hospitalization or treatment by acute health services (6, 7, 18).

2.1.4 DEFINITIONS & TERMINOLOGY: METHAMPHETAMINE ASSOCIATED PSYCHOSIS

Psychotic symptoms are commonly experienced by individuals who use methamphetamine and contribute to a significant proportion of the acute health service burden arising from use of the drug (7). As explained below, the nature and duration of psychotic symptoms experienced by methamphetamine users can vary widely, and similarly there is great variation in the clinical diagnoses or classifications that are applied to methamphetamine-associated psychotic syndromes. The way in which the syndrome is classified has implications for the understanding of the phenomenon, its epidemiology, aetiological pathways, and how it relates to primary psychosis (22). Further, there are likely to be significant differences in the treatment plan and priorities based on whether an individual with methamphetamine-related psychotic symptoms

is thought to have a primary psychotic disorder or not, with longer term care, case management and use of antipsychotic medication more likely in the former than the latter (23).

2.1.5 METHAMPHETAMINE INTOXICATION & PSYCHOTIC SYMPTOMS

Transient paranoia and hallucinations are recognized as part of the methamphetamine intoxication syndrome, characterized both in illicit users (24, 25) and in studies where the drug is administered in experimental laboratory settings (1, 26). Whilst distressing for the individual, these experiences are generally short-lived, and usually resolve within hours to days of drug use as the metabolites of the drug are excreted (27). A review of experimental studies suggested that even with high dose and prolonged use, psychotic symptoms abated in less than a week of cessation of the drug (27). A longer-lasting or more severe syndrome may meet the criteria for a methamphetamine-induced psychotic disorder (see Table 1).

2.1.6 METHAMPHETAMINE-INDUCED PSYCHOTIC DISORDER

The most widely used diagnostic systems in mental health and addiction are the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders DSM-5 (16), and the World Health Organization's International Classification of Diseases diagnostic system (ICD-10) (28). The DSM-5 defines substance-induced psychotic disorder (SIPD) as following the onset of substance use or persisting for less than one month after acute substance intoxication or withdrawal (16). The ICD-10 definition refers to psychotic symptoms that occur during or following substance use but are not explained on the basis of acute intoxication alone or a withdrawal state (28). Both systems incorporate organic exclusion criteria; that is, a diagnosis of a primary psychotic illness should not be made in the presence of a factor (such as drug use, or a physical illness) that can account for either initiation or maintenance of the psychosis. Further, a primary psychotic disorder diagnosis is considered in cases where (i) psychotic symptoms precede the onset of substance use, or (ii) there is a previous history of psychotic symptoms independently of substance use or, (iii) the symptoms are considered "in excess" of what might be expected in context of the type, amount of duration of substance use (16).

Table 1: Diagnostic criteria for substance-induced psychotic disorder

	DSM-5	ICD-10
Time frame: onset	Develops during/within 1 month of substance intoxication or withdrawal	Occurs during or immediately after (within 48 hours) of substance use
Time frame: resolution		Resolves at least partially within 1 month, and fully within 6 months of substance use
Symptoms	Prominent hallucinations or delusions	Hallucinations, delusions, abnormal affect, psychomotor disturbance
Exclusion	Not accounted for by delirium; by a disorder that is not substance induced; or if symptoms not accounted for by intoxication or withdrawal alone	

SOURCE: Adapted from DSM-5 (16) and ICD-10 (28)

Essentially, when examining psychotic symptoms in someone using methamphetamine, the key to differentiating between a diagnosis of SIPD and primary psychotic disorder is identifying whether psychotic symptoms can be causally linked to methamphetamine use. The diagnostic criteria set out in different frameworks involve parameters to assist in ascertaining the likelihood of this causal relationship, that is (i) timeline of onset (ii) timeline of resolution and (iii) nature and severity of symptoms.

Both of these diagnostic systems make a distinction between primary psychotic disorders and SIPD on the basis of (i) the chronological relationship between substance use and psychotic symptoms, (ii) the severity and type of symptoms, and (iii) the individual's history of psychotic illness (See Table 1 above). Importantly, psychotic symptoms that last for longer than a month (but less than six months) would be classified as a primary psychotic disorder by DSM criteria, but as SIPD by ICD. This difference can account for some of the variation in the prevalence of SIPD in different countries, with countries using ICD criteria having a higher prevalence. Additionally, both diagnostic systems apply these criteria across different classes of drugs to arrive at a diagnosis of SIPD, and there are no specific criteria that apply to methamphetamine-induced psychotic disorder per se. Consequently, features of the psychotic syndrome that may be specific to certain drug classes, such as tactile hallucinations or formication in amphetamine psychosis (29), are not accounted for in the diagnostic criteria.

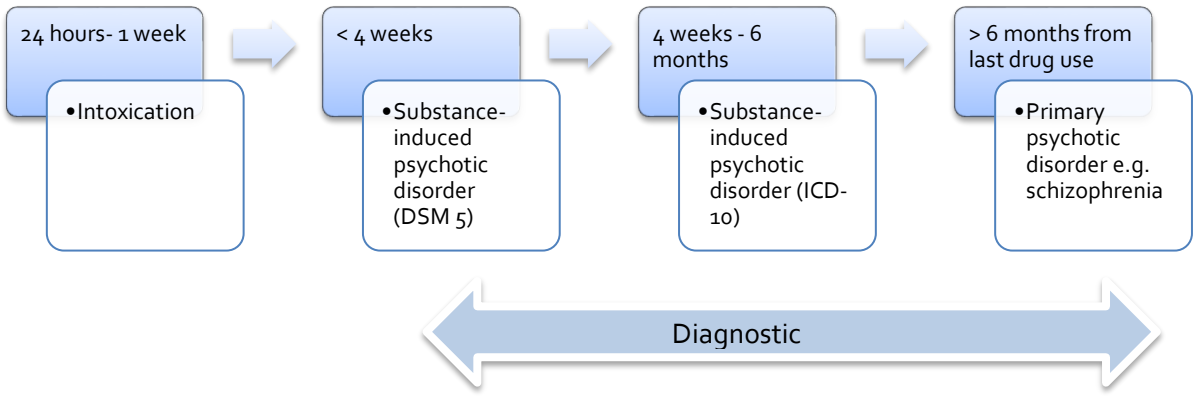

Figure 1: Diagnostic criteria for substance-induced psychotic disorder based on timeline of psychotic symptoms in relation to substance use

Notably, there is no "gold standard" diagnostic interview that operationalizes these diagnostic criteria. Commonly used tools based on the DSM-IV include both the Structured Clinical Interview for DSM-IV (SCID)(30), the Mini International Neuropsychiatric Interview (MINI)(31) and the WHO Composite International Diagnostic Interview (CIDI) (32), but they all have a degree of subjectivity in interpreting diagnostic criteria, and there is a paucity of studies specifically validating these interviews in substance use populations (33, 34). One large study found a relatively low test-retest reliability (kappa= 0.49) of current psychotic diagnoses using the SCID for DSM-III in a sample with current substance abuse (35).

In contrast, the PRISM-IV, a diagnostic interview based on DSM-IV criteria, was specifically developed for co-morbidity research in substance use (33). The tool prioritizes questions relating to substance use early in the interview schedule, with greater structure and detail in characterizing substance use history and timelines and has been demonstrated to have high test-retest reliability for current, previous and lifetime psychotic disorders (Kappas current, 0.63; past, 0.76; lifetime, 0.79) in substance use populations (33). However, only one previous studiy of MAP utilized the PRISM-IV to distinguish between substance-induced and primary psychotic disorder diagnoses (36).

2.1.7 Challenges related to terminology and diagnosis

A major challenge in the accurate diagnosis of psychotic symptoms in methamphetamine-using populations therefore relates to the substantial overlap between methamphetamine-induced and primary psychotic syndromes. The symptom profile of both disorders can be virtually indistinguishable on the basis of an acute presentation alone (37). Further, the timeframe of

both onset and resolution of symptoms is not always clear in real-world settings. Even in clinical settings with careful evaluation of the relationship between symptoms and substance use, it can be challenging to differentiate primary from secondary disorders without an extended period of abstinence (34). Many methamphetamine-dependent individuals use the drug in a daily or almost-daily pattern, making it difficult to clarify whether symptoms resolve partially or fully without any clear periods of abstinence from the drug. Symptoms that persist for longer than a month following cessation of drug use can also be difficult to classify, with authors debating whether such symptom profiles lie on a continuum between a toxic syndrome and a primary disorder (38, 39). Similarly, it is challenging to investigate the causal nature between drug use and psychotic symptoms within cross-sectional observational studies, or to exclude or control for a range of potentially confounding lifestyle factors that accompany drug use (such as sleep deprivation, poor nutritional intake, exposure to threat or stress).

A pragmatic approach used in many research studies is to utilize dimensional tools to assess psychotic symptoms that occur in samples of methamphetamine-using participants, without determining causality or substance-induced psychotic disorder diagnoses. For instance, several studies of MAP utilize instruments such as the Brief Psychiatric Rating Scale (BPRS) (40) or the Positive and Negative Symptoms Scales (PANSS) (41), both demonstrated to have acceptable validity and reliability in methamphetamine use populations (37, 42). Dimensional measures of psychotic symptoms also offer the ability to assess varying degrees of symptom severity, and to reflect changes in severity over time, potentially providing a richer and more dynamic evaluation of symptom profile (43). Alternatively, some authors have proposed the term 'methamphetamine-associated psychosis' to encapsulate the range of psychotic symptoms and acute psychosis presentations that can arise in the context of methamphetamine use. This term reflects the difficulty inferring causality between psychotic symptoms and substance use (44).

2.1.8 Terminology used in this thesis: Methamphetamine-Associated Psychosis

In this thesis, the term methamphetamine-associated psychosis, and the abbreviation MAP, will be used throughout to refer to psychotic symptoms experienced by individuals who use methamphetamine, rather than a diagnosis of methamphetamine-induced psychotic disorder.

2.2 Methamphetamine psychosis: the role of methamphetamine use

2.2.1 Methamphetamine use factors & prevalence of MAP

Given the different ways in which MAP can be conceptualized and defined, it is unsurprising that there is significant variability in its prevalence arising from differences in measurement and assessment of the outcome of psychosis across different studies. Studies that have defined MAP

as a lifetime rather than current experience of methamphetamine-related psychotic symptoms have generally reported much higher prevalence rates, in the order of 40-76% (see Table 2). Conversely, studies examining current (e.g. past month) symptoms of psychosis have found prevalence rates of MAP between 13- 24.7% (Table 2). In terms of diagnoses of methamphetamine-induced psychotic disorder, a recent meta-analysis estimated a prevalence rate of 24.5% for current diagnoses in dependent users, but this rose to 44.9% when examining lifetime prevalence (45).

Table 2: Prevalence of MAP

Study	Prevalence (%)	Outcome Timeframe	Outcome Measure
Studies measuring current symptoms or disorder			
McKetin, 2006	23	Clinically significant symptom in past year	BPRS
Lapworth, 2009	15.6	Clinically significant symptom in past month	BPRS
McKetin, 2010	21	Past year psychosis risk	Psychosis screener
Hides, 2015	24.7	Current MIPD	PRISM-IV
Zweben, 2014	4.9 current 12.7 lifetime	MIPD	MINI
Sulaiman, 2014	13 current 47.9 lifetime	Current symptoms	MINI
Studies measuring lifetime symptoms or disorder			
Chen, 2003	40	Lifetime symptoms	
Kalayasiri, 2009	46	Lifetime paranoia	MEQ
Smith, 2009	30.8-56	Lifetime	Questionnaire based on CIDI
Salo, 2013	76	Lifetime	Paranoia
Ding, 2014	35.4	Lifetime	MINI
Other outcome measures			
McKetin, 2013	60	Point prevalence of psychotic symptoms experienced at any one time-point in study (baseline, 3 months, 3 years)	BPRS

a: BPRS: Brief Psychiatric Rating Scale (40); b: Psychosis Screener (46); c: PRISM-IV (33); d: MINI: The mini international neuropsychiatric interview (31); e: MEQ: Methamphetamine experiences questionnaire (47); F: CIDI: composite international diagnostic interview (32); MIPD: Methamphetamine-induced psychotic disorder

Another potential explanation of variation in prevalence rates is the methamphetamine use patterns in the study sample. Studies conducted in recreational use populations, where individuals report using methamphetamine less than weekly for instance, have described prevalence rates of MAP of about 15% (48, 49); whereas MAP appears to be much more common in methamphetamine-dependent people in treatment-seeking populations (45, 50, 51). For instance, the prevalence of methamphetamine-induced psychotic disorder diagnoses was estimated at 43.3% in dependent samples, but only 23.2% in studies including dependent and non-dependent participants (45). This points to the centrality of MA use in MAP, and the association between methamphetamine use patterns, methamphetamine use disorder, and the likelihood of MAP.

2.2.2 PERSISTENCE OF PSYCHOTIC SYMPTOMS

There is growing evidence that a substantial proportion of people who experience a methamphetamine-induced psychotic disorder go on to be diagnosed with a persistent primary psychotic disorder such as schizophrenia (Table 3). To date, there have been five longitudinal studies examining transition from substance-induced to primary psychotic disorder diagnosis, four of which focus on amphetamine psychosis and one on methamphetamine psychosis (52).

Of the studies focussing on amphetamine, three studies utilized a linkage methodology based on national hospital discharge registers, identifying index admissions for amphetamine-induced psychotic disorder and future re-admission for primary psychotic disorder (54-56). The strengths of their design include their sample size and length of follow-up, with samples ranging from 273-825 people followed up between 8- 20 years. Only one of these studies, however, examined incident diagnoses in individuals seeking both outpatient and inpatient psychiatric treatment(55), while the others focussed on a relatively narrow sample in terms of severity of psychotic symptoms. Another limitation of the three linkage studies relates to unreliable exclusion of people with pre-existing undiagnosed primary psychotic illness. One study excluded anyone with a record of previous treatment for schizophrenia spectrum or bipolar disorder prior to the start of the study, but it is possible that people who had not sought treatment for these disorders would have been included in the dataset, and this would impact on an inflated estimate of true conversion rates(55). A small cohort study of 12 inpatients was consistent with the findings of the linkage studies, suggesting a 33% rate of conversion from amphetamine-induced psychotic disorder to schizophrenia spectrum disorder following a 6 year follow-up (53). These four studies were all conducted in Northern European populations, however- in Finland, Denmark, Norway and Scotland- all countries with comparatively lower baseline prevalence of meth/amphetamine use in comparison to Australia(57). In addition, these studies focused on amphetamine rather than methamphetamine. Although the drugs are very similar pharmacologically, the route and pattern of use of crystal methamphetamine can differ from that

of amphetamine. The commonest routes of use of amphetamine in Northern Europe are insufflation and oral use (57). In contrast, there is a high prevalence of inhalation and injecting use of crystal methamphetamine in Australia, with both of these routes associated with a high risk of psychotic symptoms (58). Similarly, the purity of amphetamine used in Northern Europe in the past decade is thought to be much lower than that of contemporary seizures of Australian crystal methamphetamine (59). Consequently, the diagnostic conversion rate in Australia may therefore potentially be higher than the 19-32% range reported in these studies.

Table 3: Diagnostic conversion from substance-induced psychotic disorder to schizophrenia

Study	n	Follow-up (years)	Conversion to schizophrenia diagnosis (%)
Kittirattanapaiboon, 2010 (52)	449	7	22
Medhus, 2015 (53)	12	6	33
Niemi- Pyttari, 2013 (54)	825	8	30
Alderson, 2017 (55)	273	15.5	19.1
Starzer, 2017 (56)	555	20	32.3

The only study that specifically focused on methamphetamine was conducted in Thailand between 2000-2007, and had a prospective cohort design, following up a sample of 1,116 people hospitalized for methamphetamine-induced psychotic disorder for 7 years. They found that 22% of the people who were able to be followed up (n=449) had been re-hospitalised and diagnosed with schizophrenia (n=100). They also found that over half (55.7%) had experienced a relapse of psychosis following their initial episode; and that 15.8% of those who could be interviewed at follow up (n=71) presented with current symptoms of psychotic disorder, based on the MINI. Further strengths arise from its sample size (n=449), with a structured diagnostic interview

assessment of psychosis outcomes at the 7-year follow-up time point adding validity to the measurement of the psychosis outcome. However, nearly half of the original sample (45%) were lost to follow-up, which may be a potential source of bias.

Taken together, this evidence suggests that about a third of people who seek treatment for meth/amphetamine-associated psychosis transition to a diagnosis of chronic psychotic disorder (schizophrenia spectrum or bipolar disorder) in the future. The evidence for this is reasonably strong, given the large sample sizes and diversity of locations in the aforementioned studies. However, almost all of the studies in this area have examined rates of conversion in cohorts initially recruited in inpatient psychiatric units. The selection of hospitalized cases may therefore result in ascertainment bias or Berkson's fallacy, with the true rate of diagnostic conversion in the population potentially lower. On the other hand, the rate does not account for those individuals with sub-threshold methamphetamine-associated psychosis experiences who may not have sought treatment, and the trajectory for such individuals remains unclear.

2.2.3 Methamphetamine use & neurochemical changes associated with methamphetamine use disorder and methamphetamine-associated psychosis: a focus on dopamine

The effect of methamphetamine (and other ATS) on the dopamine system is considered to be critical to both its acute reinforcing effects and abuse liability. The dopamine theory of addiction, first raised over forty years ago, frames dopamine-mediated neurotransmission within the mesocorticolimbic 'reward' circuitry as central to the establishment and maintenance of addiction (57). Despite considerable debate as to whether this theory holds true for some drugs(57), there is substantial evidence underpinning its relevance to stimulant drug dependence, including methamphetamine and other ATS. The potentiation of dopamine neurotransmission by acute methamphetamine use causes strong reinforcement of drug use in the short term(14), but in contrast, several studies suggest long-term methamphetamine use is associated with dopamine depletion and hypofunction, particularly in the striatum(11, 15). A recent meta-analysis of functional neuroimaging studies by Ashok and colleagues provides the most up-to-date evidence on changes in dopamine transmission in methamphetamine dependence, finding a significant decrease in striatal dopamine transporter availability and D_2/D_3 receptor availability in methamphetamine-dependent individuals, with evidence for both presynaptic and post-synaptic downregulation of the striatal dopamine system in long-term methamphetamine users (15). While this review provides very useful insights into the function of the dopamine system following illicit recreational use of methamphetamine, it does have a number of limitations. The included studies all recruited participants who had been abstinent from methamphetamine for periods ranging between from between one week to up to 1 ½ years. Given that there may be potential changes in neurotransmitter function during methamphetamine withdrawal and following remission (58), it is unclear whether dopamine function in withdrawing or long-term abstinent individuals reflects

the same state as people who are actively using the drug. Secondly, participants in the included studies all had co-morbid nicotine abuse or dependence. Although this is an accurate representation of methamphetamine-using populations in the community, it may impact on the underlying nature of the relationship between methamphetamine and its effect on dopamine function.

The dopamine system also plays a critical role in the pathways thought to underpin psychotic symptoms. For over half a century, the dopamine hypothesis of schizophrenia has been the prevailing theory on the pathogenesis of psychotic symptoms in the illness. Briefly, dopamine is thought to be the primary neurotransmitter contributing to psychosis based on evidence that (i) antipsychotic medications block dopamine (D2) receptors and (ii) dopamine agonists promote positive psychotic symptoms(59). Further, neuroimaging studies have demonstrated that individuals at high risk of developing psychosis have dopaminergic abnormalities, at a lower level than that observed in schizophrenia, bolstering the concept of dopamine dysfunction underpinning 'psychosis proneness' (60). In recent times, there has been some debate regarding the centrality of dopamine to the evolution of psychosis (61) in view of evidence that other neurotransmitter systems, such as the glutamate (62) and serotonin (63) systems may also play a role. However, stimulant-induced psychosis has been promoted as a model for schizophrenia based on its dopaminergic effects, drawn from evidence from amphetamine administration in experimental settings triggering both paranoid psychotic symptoms and striatal dopamine release (59, 64). While the effects of methamphetamine on serotonin and glutamate pathways may also have some impact on driving methamphetamine-associated psychotic symptoms, there is considerably less evidence for this in contrast with the available literature on dopamine (59), and so the following section focusses on a discussion of methamphetamine-related dopamine dysfunction and its relevance to psychosis.

Individuals with a history of an episode of MAP often present with a lasting vulnerability to a recurrence of the disorder, both in the setting of a relapse to methamphetamine use, or with social stress (65, 66). Indeed, most individuals who use methamphetamine develop a psychotic illness after repeated use of the drug and prolonged exposure. One explanation for this phenomenon is the process of dopamine sensitisation, whereby repeated administration of methamphetamine results in reversed tolerance, with a greater response of striatal dopamine receptors resulting in progressively greater dopamine release with exposure over time (67, 68). The challenges of investigating sensitisation in human illicit drug use populations are numerous, given the difficulty in separating out the effects of stimulant use from other drug use(69), unreliability in estimation of drug dose and dynamic patterns of use, and the paucity of prospective longitudinal studies examining changes in vulnerability and propensity to psychotic symptoms over time. However,

this concept has long been supported by acute administration studies in both animals (70) and healthy human participants (71, 72). A 2004 systematic review by Curran and colleagues found limited evidence for sensitisation in illicit stimulant-associated psychosis, but reported on two experimental administration studies that directly support this phenomenon(69). A subsequent study in 2006 by Boileau and colleagues utilised [^{11}C]Raclopride tracing and positron emission tomography (PET) to measure dopamine release, and found that when healthy participants (n=10) were repeatedly administered dextroamphetamine, they had greater striatal dopamine release with each progressive increase in dose; they also continued to have an elevated striatal dopamine response to amphetamine up to 1 year later (71). O'Daly and colleagues investigated this further by assessing subjective, cognitive, behavioural and physiological responses to a sensitising dosage pattern of dextroamphetamine in a randomised, double-blind, placebo-controlled study of 22 healthy volunteers (73). Their results supported subjective and behavioural sensitisation effects of repeated doses of dextroamphetamine, as well as imaging evidence of sensitisation reflected by medial temporal lobe hyperactivity. While this was a small study, it provided an important contribution to the contemporary evidence linking dopamine dysfunction with cognitive theories of psychosis, an area that is likely to grow with evolution in neuroimaging technology.

While neuroimaging evidence on dopamine function would help inform our understanding of sensitisation and its relevance to the pathogenesis of MAP, the majority of imaging studies in methamphetamine use populations have excluded participants with mental illness, or people who have experienced methamphetamine-associated psychosis (15). To date, only two functional neuroimaging studies examining dopamine neurotransmission have been conducted on people with MAP(74, 75). Iyo and colleagues PET study of six men with methamphetamine dependence who had been abstinent for one month and had a lifetime history of MAP, compared to healthy controls, The study found no difference in striatal D2 receptor availability compared to healthy controls (74).

Another PET study by Sekine and colleagues utilized using 2-β-carbomethoxy-3β-(4-[^{11}C] fluorophenyl) tropane, a dopamine transporter ligand, as a tracer to examine dopamine function in 11 methamphetamine-dependent individuals, and found a correlation between positive psychotic symptoms of MAP and a reduction in striatal dopamine transporter density (75).

Taken together, the literature suggests that short-term methamphetamine exposure is associated with acute increases in dopamine and a range of other neurotransmitters (noradrenaline, serotonin), but in the long-term, repeated exposure likely results in a hypo-dopaminergic state. Given the limited number of studies specifically focussing on people with psychotic symptoms, it is still unclear whether the same neurochemical changes occur in MAP as well, or whether

methamphetamine-mediated changes in neurotransmission relate to symptom subtypes and presentations.

2.2.4 PHENOMENOLOGY

The terminology applied to psychotic symptoms is generally derived from the understanding of schizophrenia and arose from studies attempting to delineate different clinical subtypes within the disorder, within the recognition of schizophrenia as an essentially heterogeneous entity. Andreasen and colleagues first explored the benefits of subtyping schizophrenia into positive and negative syndromes. They defined positive symptoms as including hallucinations, delusions, thought disorder and disorganized speech and behaviour; conversely, negative symptoms referred to affective flattening, alogia, avolition, anhedonia and attentional impairment (76). This terminology has been widely accepted as a consistent way of conceptualizing the predominant presenting syndrome in psychosis (77), and has been found to relate to prognoses and functioning (78, 79). For example, people with mainly negative symptoms have been found to have poorer long-term functional outcomes, and marked cognitive impairment (78). This means of classification has also led to the development of a range of validated tools to assess psychotic symptoms, such as the Positive and Negative Symptom Subscales (PANSS)(41) and the Brief Psychiatric Rating Scale (BPRS)(80). These tools are used in the assessment of other psychotic syndromes beyond schizophrenia, such as drug-induced psychoses like MAP.

Initial studies of people with MAP suggested that psychotic symptoms in the context of intoxication with methamphetamine were initially considered indistinguishable from an acute psychosis related to schizophrenia (81, 82), with auditory hallucinations and suspicious or paranoid delusions found to be the most common feature of both presentations. Visual and tactile hallucinations and particularly formication - the sensation of insects crawling under the skin- are reported to be more common in MAP in comparison to other types of psychoses (83). However, the majority of people with MAP do not experience such symptoms.

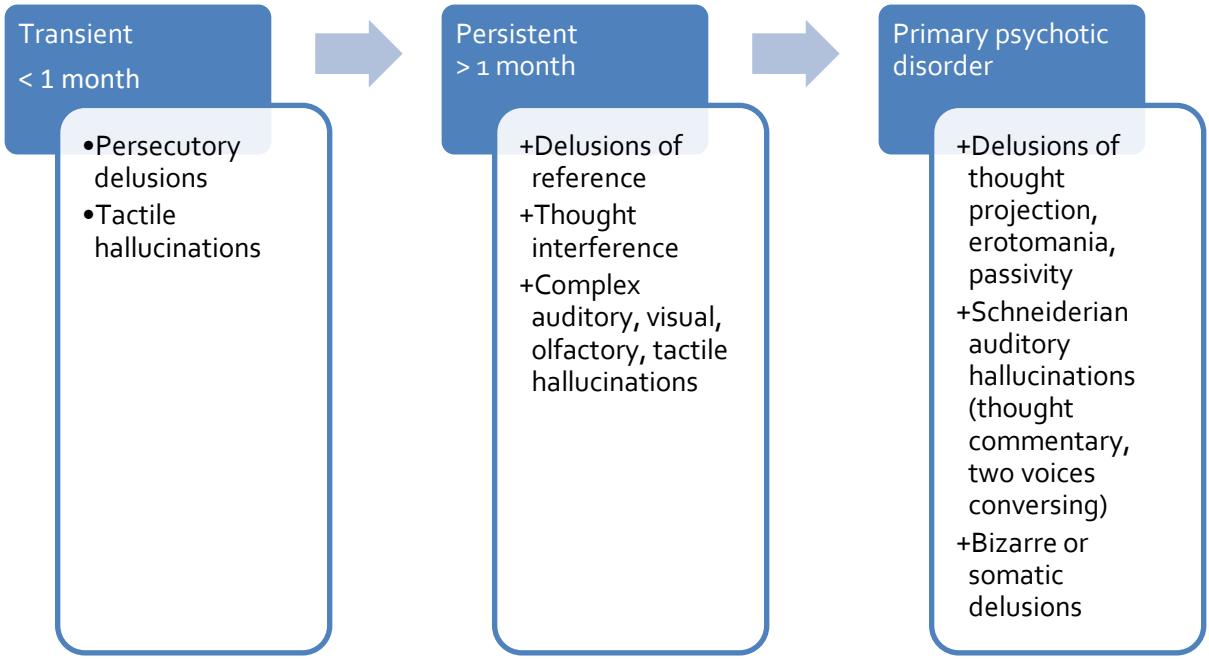

Figure 2 Symptom profiles in transient and persistent MAP and primary psychotic disorder
Adapted from Mcketin et al, 2017 (84); McKetin et al, 2018 (85)

However, studies from Japan and Taiwan, where MA use has been widespread for the past two decades, suggest that MAP is a heterogeneous syndrome with a range of presenting symptoms types and severity (23, 86, 87). Over time, it has become clearer that negative and first-rank symptoms do occur in MAP (88, 89) and that acute presentations of MAP often include the full spectrum of symptoms seen in schizophrenia (37, 90). Recent evidence suggests, however, that there may be differences in symptom profile between methamphetamine dependent individuals with transient psychotic symptoms, those with more persistent disorders, and individuals who meet criteria for a primary psychotic disorder (See Figure 2) (84). Further, one study suggested that these differences may be present from the initial experience of psychotic symptoms, suggesting that symptom profiles could assist in distinguishing 'psychosis-prone' individuals at risk of later development of a more persistent disorder (85). This evidence is based on individuals' retrospective recall of phenomenology from antecedent psychotic experiences, with a bias arising from those with limited insight into their illness or symptoms. While replication is therefore required in prospective studies, this study does provide preliminary evidence towards characterisation of an individual's risk profile and trajectory to primary psychotic disorder.

2.2.5 MAP AND THE PSYCHOSIS CONTINUUM

While the prevalence of clinical psychotic disorders in the general population is relatively low (ranging from about 2-3%), there is increasing evidence that subclinical psychotic experiences, such as hallucinations, paranoia and suspiciousness, may be much more prevalent (91-93). Such

evidence has contributed to a shift in the understanding of psychosis over the past decade, toward a more dimensional view of psychotic experiences along a continuum of frequency and severity, ranging from common low-threshold experiences such as suspiciousness, to full-blown psychotic disorders associated with distress and help-seeking behaviours (93). Indeed, there is considerable debate about the centrality of psychotic symptoms themselves in the diagnoses of primary psychotic disorders such as schizophrenia and bipolar disorder, with some arguing that psychotic experiences are non-specific markers that map to a broad range of syndromes and illnesses (94).

> "Indeed, the brain generates hallucinations and delusions in so many conditions that it is difficult to understand how these symptoms have maintained primacy in the diagnosis of any specific disease. Psychotic experience is to the diagnosis of mental illness as fever is to the diagnosis of infection—important, but non-decisive in differential diagnosis." Fischer and Carpenter (94)

The role of drug use within this model remains poorly understood. Some drugs- including methamphetamine and cannabis- are widely accepted to be 'psychotogenic', and have a propensity to trigger psychotic disorders in individuals with a predisposition to psychosis symptoms (22, 95, 96). It is still unclear whether such 'substance-induced' psychotic syndromes are disparate entities compared to primary or schizophreniform psychoses, with different phenomenological characteristics, or whether they sit along a continuum of psychotic experiences and share the same risk and aetiological factors (22, 64, 96, 97). This uncertainty is reflected in the contemporary literature, with some authors suggesting there should be a shift of classification of substance-related psychosis, from "substance-induced" to "substance-associated" psychosis(22).

This concept of a continuum of psychosis experiences also has implications for aetiology and risk factors associated with the development of psychosis, or 'psychosis proneness'(92). A range of environmental risk factors has been identified to be associated with full-blown clinical psychotic disorders such as schizophrenia- such as urbanicity, migration, childhood adversity or trauma(98). However, it is unclear whether sub-threshold or mild symptoms are driven by these same risk factors (92, 93). There are few studies that have explored the role of these risk factors within substance-induced psychosis, and specifically, methamphetamine-associated psychosis, so this remains a critical gap in knowledge.

2.2.6 Risk Factors and Correlates of MAP

While it is widely recognized that methamphetamine is a substance that can trigger psychotic symptoms, the correlates and risk factors for development of MAP remain unclear.

In animal studies, the administration of amphetamine and methamphetamine was historically used as model of schizophrenia (99). Subsequently, early human studies demonstrated that the

administration of increasing doses of amphetamine could trigger psychotic symptoms even in healthy individuals with no history of substance use or mental health problems (1, 26, 82). However, even in these experimental settings, there appeared to be a subset of individuals who remained resilient to developing psychotic symptoms. Conversely, others were particularly vulnerable, with psychotic symptoms triggered at lower doses of the drug. This phenomenon has since been seen in all the observational studies of MAP to date. Although some studies have suggested a dose-response relationship between methamphetamine use and psychosis symptoms (42), others have failed to replicate this (48, 100), suggesting that methamphetamine use alone may not be sufficient to trigger psychosis. Consequently, the role methamphetamine use itself plays in triggering and maintaining psychotic symptoms in MAP requires further investigation.

2.2.7 Limitations and Gaps in understanding Correlates of MAP: What is the role of MA use as a correlate of MAP?

In order to understand the role of MA use as a risk factor of MAP, a range of key gaps and limitations in the methodology of existing studies need to be acknowledged. While the gold standard methodology for investigating risk factors would be to examine evidence from prospective longitudinal cohort studies, there are clearly significant practical and logistical difficulties in conducting this type of study to examine the effects of drug exposure. Consequently, the majority of the literature in this area comprises of cross-sectional observational studies, and this study design obviously limits the ability to draw inferences regarding causation or the nature and direction of the association between predictor variables and psychosis.

Many studies have involved comparisons of methamphetamine users with psychosis with healthy control subjects, rather than with other methamphetamine users, which makes it difficult to determine if differences between groups have arisen as a result of methamphetamine use alone, or due to other factors. As discussed above, variability in the definition, measurement and timeframe of assessment of the outcome of psychosis also impacts on the ability to synthesise the results of existing studies. The majority of the literature comprises of studies that measure lifetime experiences of psychosis based on retrospective recall, rather than current psychotic symptoms. This approach not only raises the risk of measurement error, but also limits the ability to examine the relationship between patterns of methamphetamine use and fluctuating psychotic symptoms.

Another significant limitation in extant literature relates to the lack of representativeness of recruited samples. Many studies of MAP to date are subject to selection bias and comprise non-representative samples. Several studies have been conducted in hospitalised psychiatric inpatient samples (47, 51, 101) and therefore have measured more severe psychotic symptoms that have necessitated psychiatric treatment. Similarly, other studies have been based in detention or residential rehabilitation settings, recruiting individuals with heavier MA use, more severe

dependence, and a longer duration of use (47, 101-103). In contrast, methamphetamine-using adults in the community and non-treatment seeking settings present with variable patterns of methamphetamine use, dependence or other drug use leading to difficulties in extrapolating the results of existing studies. It remains unclear whether the risk factors for MAP demonstrated in heavy use populations with severe psychotic symptoms can be extrapolated to outpatient and community samples presenting earlier in their trajectory of drug use, with sub-clinical symptoms.

In terms of acute presentations of MAP, what is missing is data on a broader pre-hospital sample, reflecting a wider variation in both psychotic symptom profile and in severity of methamphetamine use, in comparison to hospitalised datasets. One way to examine this is to investigate social and demographic correlates of MAP in presentations to ambulance services. This broadens the sample to acute presentations that are severe enough to meet clinical significance and to require treatment; but on the other hand, not severe enough to require hospitalisation, as only a subset of ambulance presentations would translate to hospital admissions. No previous studies have examined psychosis presentations in methamphetamine-using adults in pre-hospital or ambulance datasets. Correlates of MAP in this sample could be compared to correlates of primary psychotic disorder in order to ascertain factors that reliably distinguish between these acute presentations. Such information would be of direct clinical relevance, assisting frontline workers with diagnostic clarification.

In addition, studies of outpatient methamphetamine treatment-seekers are largely missing from existing literature. Treatment-seeker samples recruited in previous studies, as mentioned above, have often been from residential or detention settings. While a few studies have been conducted on outpatient treatment-seeking samples, these have been from 'mainstream' alcohol and other drug treatment services (42). There is a recognized treatment delay and 'treatment gap' for methamphetamine use, with only a small proportion of dependent users having contact with alcohol and drug treatment services (5). People often present for treatment late in their trajectory of use, with the largest Australian study to recruit adults seeking outpatient treatment for methamphetamine use had a sample with a mean duration of use of 13.1 years (42). Consequently, while the existing literature supports methamphetamine use as a key factor in driving MAP risk, this literature is drawn from studies of heavily dependent individuals with a long duration of use. It is not clear whether methamphetamine use factors play a central role in people presenting earlier, with less severe dependence. This is particularly important in informing treatment responses outside of 'mainstream' alcohol and other drug treatment, for instance, in primary care or acute health settings. People who use methamphetamine often present to such settings with acute harms, but are not treatment-seeking; these presentations offer an opportunity to intervene early (104). Studies conducted within early intervention or stimulant-specific specialist services

offer a means of exploring the role of methamphetamine use in samples with less severe dependence, but no studies to date have investigated methamphetamine psychosis in such services.

Finally, given the wide variation in the definition and measurement of MAP across studies, what is needed is a systematic and comprehensive review of the existing literature to clarify the role of methamphetamine use in MAP. Although previous reviews have been conducted on this topic, they have not been systematic in methodology and have not specifically appraised the quality of the literature (22, 23). This is an essential gap that contributes to uncertainty in this area, in both clinical and research settings.

2.3 Cognition, Psychosis and Methamphetamine use

Following on from appraisal of role of methamphetamine use as a key risk factor for MAP, the second aim of this thesis is to identify cognitive markers of psychotic symptoms in methamphetamine-using adults. The following section explores the literature on what is known about cognition and psychosis, and cognition in methamphetamine dependence, concluding with a summary of the key gaps in this area and research questions.

2.3.1 Cognition and Psychosis Proneness

Some authors have proposed the potential use of cognition as a marker of psychosis proneness (105). Characteristic cognitive impairments have been observed in chronic primary psychotic disorder populations, in first-episode psychosis, in 'pre-psychotic' prodromal or clinical high-risk cohorts, and in unaffected first-degree relatives of people with psychotic illness (105). Consequently, there is a growing literature exploring the use of cognition as a 'trait' marker for psychosis vulnerability, and it could represent similar promise in the study of substance-induced psychotic disorders such as MAP.

2.3.2 Cognition and Schizophrenia

Cognitive impairment is now widely recognized as a core feature of schizophrenia and it is well established that individuals with schizophrenia have a range of deficits across all domains of cognition in comparison with healthy participants, with the most pronounced impairments characterised in processing speed and working memory (106-108). Treatment with anti-psychotic medications has been considered to play a role in the extent of cognitive deficits, but even meta-analyses on drug-naïve schizophrenia cohorts have suggested a significant degree of impairment (109).

Several studies in clinical high risk (CHR) for psychosis cohorts have identified that neurobiological deficits exist pre-morbidly in psychosis-prone individuals, that is, before a first episode of psychosis (FEP) (110, 111). CHR populations are considered in many ways to be an

'intermediate' in between unaffected first degree relatives and individuals with psychotic disorders (110). Over the past three decades, the definition of high risk for psychosis cohorts has been refined into contemporary instruments mapping criteria that reflect familial and genetic liability to psychosis, and the experience of brief or attenuated psychotic symptoms (110), characterizing a population that is estimated to have up to 400 times greater risk of developing primary psychotic disorders (predominantly schizophrenia) than the general population (60). Importantly, two large meta-analyses of CHR cohorts (n=1888 and n=1215) provide evidence of widespread cognitive deficits in participants before first experience of psychotic symptoms, and before treatment with antipsychotic medication (112, 113). While there is some degree of heterogeneity in outcomes observed in different studies, small-medium sized impairments have been reported across all cognitive domains in comparison with healthy controls, with the greatest degree of impairment in verbal and visual memory (112, 113). Both these meta-analyses found a greater degree of cognitive impairment in CHR individuals who subsequently transitioned to development of a full-blown psychotic episode (First Episode Psychosis or FEP), compared to prodromal participants who did not transition, with moderate-large effect sizes particularly observed in domains relating to verbal fluency, and verbal and working memory (112, 113). One study of an UHR cohort found that a combination of tasks of verbal memory could potentially predict transition to FEP with a sensitivity of 0.75 and a specificity of 0.79 (114), whilst another used an integrated model of psychotic symptoms and cognition (speed of information processing) to derive a sensitivity of 0.83 and specificity of 0.79 for prediction of transition (115). In summary, these findings add weight to the concept of cognition as a marker of psychosis proneness in CHR populations.

There is a widely held view that schizophrenia is a progressive neurodegenerative disorder, and that cognitive impairments that are present at onset continue to worsen with stage and severity of illness. However, this may not be the case, and a meta-analysis of 25 studies (n=1870) provided evidence that cognitive impairments present in 'pre-psychotic' or prodromal CHR populations do not worsen over time, supporting the idea of stability in cognition before and after onset of psychosis and challenging the concept of neurodegeneration and cognitive decline in schizophrenia (116). In addition, a systematic review of 26 longitudinal studies of cognitive impairment in FEP populations showed that such cognitive deficits appear to remain relatively stable from the point of FEP over periods of up to ten years, despite progression of structural brain changes or psychopathology (117).

In summary, these findings suggest that cognitive deficits in a range of domains could relate to a vulnerability to psychosis, and an underlying neurobiological process that promotes this vulnerability. As some authors have proposed, cognitive impairment could be a promising trait marker of psychosis proneness (105, 110, 111, 114).

2.3.3 SOCIAL COGNITION AND PRIMARY PSYCHOSIS

Social cognition has been defined as both the emotional and cognitive functions necessary to understand and predict other people's behaviour or mental states (118, 119). Based on the results of a National Institute of Mental Health's Consensus Committee, social cognition can be thought to comprise of four key domains: "emotion perception and processing, social perception and knowledge, attributional bias, and Theory of Mind" (119). It has emerged as a core domain of research into schizophrenia and other psychotic disorders in the past decade. While there is an extensive literature supporting the role of social cognition in schizophrenia and other psychotic disorders (119, 120), this has not previously been examined in the study of substance-associated psychosis.

In populations with schizophrenia, impairment in social cognition is a robust finding across numerous cross-sectional studies in diverse patient groups, with associations found with severity of illness and or symptom domains (positive and negative symptoms) (120, 121). Furthermore, social cognition has been found to correlate with functional outcome in people with psychotic disorders (122), with some studies supporting a stronger association with real-world functioning than other aspects of neurocognition (122, 123).

Deficits in social cognition have been shown to be present in both CHR (110, 124) and FEP cohorts, suggesting that these impairments may be pre-existing, and could be independent of the stage of psychotic illness (125). A meta-analysis of 22 studies, including 1229 individuals meeting CHR criteria and 825 healthy controls, found a medium effect size for impairment in social cognition (g=-0.477) in the CHR group compared to controls(124). Importantly, the authors highlighted that there appears to be a much greater effect size for deficits in social cognition (g=-0.477) in comparison to neurocognitive deficits (g=-0.344) in CHR populations (124). In summary, existing studies appear to support the role of impairment in social cognition as a 'trait' rather than 'state' phenomenon in schizophrenia (124, 126), and several authors have put forward the possibility of social cognition as a useful vulnerability marker for schizophrenia and other chronic psychotic disorders.

Therefore, if impairment in cognition and social cognition represent a promising vulnerability marker for non-substance related psychosis, this raises the question of whether the same may be true in substance induced psychoses, and specifically in MAP.

2.3.4 COGNITION AND METHAMPHETAMINE USE

The relationship between cognition and psychosis is less clear when considering substance-induced psychosis, as many substances have independent effects on cognition even in the absence of psychotic symptoms. This is particularly the case for methamphetamine and other stimulant

drugs, with a growing body of literature exploring the neurocognitive impairments associated with chronic methamphetamine use (127).

The acute administration of methamphetamine exerts potent effects on a variety of CNS neurotransmitter systems, including the dopaminergic, serotonergic and GABA-ergic systems (14, 128, 129). Long-term methamphetamine use has been shown to cause neuroadaptation, particularly in dopaminergic nigrostriatal pathways (129). There is now considerable evidence supporting cognitive deficits in people with methamphetamine use disorder. Three reviews and meta-analyses have demonstrated that methamphetamine-dependent individuals present with impairment on a wide range of cognitive domains compared to healthy controls (127, 129, 130). On the other hand, there has been some debate about the nature, magnitude and meaningfulness of these findings (131, 132).

The first systematic review and meta-analysis in this area was conducted by Scott and colleagues in 2007 and included 18 studies of 951 participants (487 with methamphetamine abuse or dependence; and 464 healthy controls) (129). They found evidence of impairment in cognitive performance across nine domains: reaction time, attention/working memory, executive function, learning, memory, language, speed of information processing, motor skills and visuo-construction. The review identified medium effect sizes for impairment across most of these domains, and in particular, for executive function, speed of information processing, episodic memory and motor function. While the review was comprehensive and systematic, it was limited by the number of studies available at the time, with significant gaps in the domains tested, as none of the included studies investigated impulsivity or decision-making, social cognition or the impact of mental health symptoms and co-morbidities on cognitive performance in methamphetamine-using populations.

In contrast, Hart and colleagues published an alternative perspective on cognition in methamphetamine use populations. They identified that existing studies of cognition in methamphetamine use populations often had poorly-matched control groups. All existing studies, being cross-sectional in design, were limited in their ability to examine an association between cognition and methamphetamine use. Further, they argued that the degree of cognitive deficits identified in previous reviews, while statistically significant, may not have been clinically or functionally significant and could have been considered within normal range if examined with reference to normative data (131). Their critique was the first to point out that when investigating cognitive performance in methamphetamine-using adults, adjustments need to be made for pre-morbid IQ or education, as well as comparison against age and education matched healthy controls.

In response, a subsequent review by Dean and colleagues (130) aimed to specifically examine if methamphetamine use could be causally linked to cognitive impairment, and whether the severity of methamphetamine use disorder was associated with a greater degree of cognitive deficits. However, they failed to identify any longitudinal studies that could address this question and did not find any relationship between the dose or severity of methamphetamine use and level of cognitive impairment. Nevertheless, their results were consistent with that of Scott's 2007 review, demonstrating evidence of widespread cognitive impairment in people with methamphetamine use disorder.

Most recently, Potvin and colleagues sought to address some of the concerns raised by Hart in their 2018 systematic review and meta-analysis (127). They synthesised the results of 44 studies of 1592 people with methamphetamine use disorder, and 1820 healthy controls (total n=3412). Importantly, they included studies that examined both impulsivity and reward-based decision-making, and social cognition, a gap in previous reviews to date. They found that people with methamphetamine use disorders had moderate cognitive impairments across a number of domains but that the greatest degree of deficit was observed for impulsivity and reward-based decision-making (n=8 studies, effect size estimate Cohen's d=0.926 (95%CI 0.716-1.135)), and on tasks relating to social cognition (n=3 studies, effect size estimate Cohen's d=1.117 (95%CI 0.810-1.423)). The individual studies investigating social cognition are discussed in further detail below. The authors of the review used meta-regression analyses to adjust for a range of confounding variables, including age, sex, length of abstinence and level of education and did not find any impact of these variables on the association between methamphetamine use disorder and cognitive performance. This comprehensive, rigorous and large-scale review provides up-to-date convincing evidence of a link between methamphetamine use and cognitive impairment. However, as with previous reviews, psychotic symptoms or diagnoses were not measured or accounted for, and so it is unclear how the cognitive impairments identified in meta-analyses translates to individuals with methamphetamine-associated psychosis.

In summary, in terms of specific domains, Potvin and colleagues provide an overview of the key domains found to be impaired in studies of methamphetamine-using participants to date (130). Specifically, of the 44 studies included in the Potvin meta-analysis, the following cognitive domains were found to be impaired in methamphetamine-using participants in comparison to healthy controls (ordered by effect size (Cohen's d)); impulsivity (0.926), verbal learning (0.587), working memory (0.509), executive function (0.486), visual memory (0.473), global cognition (0.462), verbal fluency (0.426), attention (0.425), verbal memory (0.400), visuo-spatial ability (0.387), processing speed (0.336), and visual learning (0.275). These results from Potvin's synthesis contribute to the methodology of the studies planned in this thesis.

2.3.5 SOCIAL COGNITION AND METHAMPHETAMINE USE

Four studies to date have assessed social cognition in methamphetamine use. Three were included in the Potvin meta-analysis mentioned above, and in combination, their results suggested that the domain of social cognition (and specifically, emotion recognition) was the cognitive domain identified with the greatest magnitude of deficit in methamphetamine-using participants in comparison with healthy controls (Cohen's d 1.117, p=0.0001, correlating with a large effect size). A fourth study, not included in the Potvin meta-analysis, included neuroimaging data that provided further insight into emotion recognition deficits. The findings of individual studies are discussed here.

The first study was conducted in 2009 by Henry and colleagues in Australia, assessing abstinent former-users of methamphetamine in community rehabilitation against healthy controls. They found that individuals with a history of methamphetamine dependence were impaired on both emotion recognition and theory of mind tasks (133). This study was the first to demonstrate that methamphetamine use may be associated with deficits in social cognition that were present even six months following abstinence from the drug. As a cross-sectional study, it was unable to determine if these deficits were present prior to substance use, or a result of use. The study was limited by its small sample size (n=12), and by strict exclusion criteria that impacted on its external validity- people with a current or previous psychiatric disorder (screened from medical record), or current or previous substance dependence were excluded. Indeed, approximately 80% of potentially-recruitable methamphetamine-dependent individuals were excluded from the study on the basis of these two exclusion criteria.

The second was a study of 28 Korean men with methamphetamine abuse (5 of whom met criteria for methamphetamine dependence), recruited from an inpatient drug rehabilitation unit, compared against 27 healthy controls (134). They found that the cases performed worse than the healthy control group on both FER and ToM tasks, and also correlated poor performance on social cognition with impairments in cognitive flexibility, as measured by the Wisconsin Card Sorting Test (WCST). This study extended the findings of Henry and colleagues in a larger sample of more recently abstinent individuals with mixed severity of use and dependence. However, this study also had strict inclusion criteria, and excluded participants with a history of any other substance use (other than caffeine or nicotine), and those with a current or previous Axis I psychiatric diagnosis other than methamphetamine use disorder.

Zhong and colleagues conducted a prospective study on a group of 54 methamphetamine-using participants in a compulsory detention centre in China, compared against 58 healthy controls (135). They assessed a range of cognitive domains, one of which was emotion recognition (*Social emotional cognition task- SEC)*, measured by identification of different facial expressions from a

choice of four faces. Participants were then re-tested at three and six months (with considerable attrition, n= 44 (81%) methamphetamine users at three months and n= 35 (65%) at 6 months). Details regarding the task itself were limited. The authors did not explain whether this emotion recognition task was sensitive to practice effects at the follow-up time points; however, the healthy control participants did not show improvement in the measure from the baseline to third assessment, which the authors suggested demonstrated a lack of practice effect. The key finding from this study was that at baseline, methamphetamine-using participants had significantly poorer emotion recognition relative to healthy controls, but that this improved substantially within three months (with further improvement to six months), to the point that there was no difference between recovering participants and healthy controls at six months. Notable limitations of this study include the lack of age and education matching between methamphetamine-using participants and controls, and a significant difference between the groups in education level. Pre-morbid intelligence and/or education level was previously highlighted by Hart and colleagues as an important confounder in studies of cognition in methamphetamine dependence (131).

Finally, Payer and colleagues conducted a functional MRI study (fMRI) of 12 MA-dependent participants while they performed a facial affect matching task(136). They did not find any differences between the MA-dependent individuals and healthy control participants in performance on the facial affect matching task. However, they identified differences in the cortical regions activated on fMRI whilst exposed to fearful or angry faces in the MA-dependent group versus healthy control participants, with MA-dependent people showing greater activation in the dorsal anterior cingulate cortex region, and lower activity in the ventrolateral prefrontal cortex (VLPFC) region. The MA-dependent participants were in the early stages of abstinence (between 5-16 days since last use) and were not dependent on any other drugs other than nicotine. The study utilized “Emotion Match trials” that used stimuli selected from the Ekman and Friesen face set, but only displayed faces classified as having fearful, angry or neutral expressions. This small study was likely underpowered to detect any differences in facial emotion recognition but provided novel imaging evidence of differences between MA-dependent and healthy control individuals. As with the studies conducted by Kim and Henry, this study excluded any participants who were dependent on drugs other than nicotine, and participants with a current psychiatric disorder.

In summary, these studies suggest impairment in social cognition in abstinent individuals with a history of methamphetamine use disorder, as compared to healthy controls. However, the restrictive samples in these studies limit the generalizability of these findings to real-world populations. In general, these studies have not measured or examined psychosis symptoms, or any other psychopathology; rather, the focus has been on the relationship between emotion

perception and patterns of substance use. Consequently, there is a significant gap in our understanding of social cognition in methamphetamine-associated psychosis.

2.3.6 COGNITION AND METHAMPHETAMINE-ASSOCIATED PSYCHOSIS

As discussed in the introductory chapter, the few studies that have focused on individuals with methamphetamine-associated psychosis suggest that MAP is associated with particular cognitive impairments that (i) differ from healthy controls, (ii) differ from individuals with methamphetamine dependence without psychosis and (iii) do not differ from individuals with schizophrenia (137-140). While no reviews or meta-analyses have synthesised the evidence on cognition in methamphetamine-associated psychosis, the following four individual studies provide some insight into the relationship between cognition, methamphetamine use and psychotic symptoms. No previous studies have examined social cognition in methamphetamine use populations.

Jacobs and colleagues were the first to explore cognition in MAP, examining the cognitive profiles of 20 adults with psychotic symptoms following MA use, to 19 controls with a history of chronic paranoid schizophrenia (138). They tested the following cognitive domains - attention, learning, memory, executive functioning, speed of information processing and general intellectual functioning - and found similar impairments in both the MAP and schizophrenia groups with no significant differences between groups on any cognitive domain. Importantly, the study did not examine the frequency of methamphetamine use or the severity of methamphetamine dependence in the MAP group, so the findings of this study do not assist in understanding the impact of MA use patterns on cognitive impairment in the MAP sample. Limitations of this study included a small sample size, and the high proportion of both case and comparison groups receiving antipsychotic medication, which is recognized to impact cognitive function (141). Case and comparison subjects were not matched on potentially relevant confounding factors (e.g. age, intellectual functioning), and multivariate analyses were conducted without adjustment for such confounders. While these limitations could have accounted for the negative result of this study, the alternative explanation is that the MAP group in this study *did not* differ from the schizophrenia group, and that they were both similar in terms of cognitive profiles.

An Iranian study replicated these findings in a sample of adults with MAP, compared to those with chronic schizophrenia, and healthy controls (137). Ezzatpanah and colleagues recruited 30 inpatients with current symptoms of MAP who sought treatment in an emergency department and compared them to 30 people with a history of chronic schizophrenia, and 30 age, gender and education-matched healthy controls. The cognitive battery included tests of executive function (Wisconsin Card Sorting Test), selective (Stroop) and sustained (Visual Search and Attention Test-VSAT) attention, and memory (Wechsler Memory Scale). They found no statistically significant

differences in cognitive performance between the schizophrenia and MAP groups in all tasks except the VSAT; and with both groups having significantly poorer performance than healthy controls on all the cognitive tasks. While some characteristics of the methamphetamine use patterns of the MAP group were reported (average duration of use 10.88 (SD=17.82) months), no further analysis was conducted to examine any associations between cognitive performance and methamphetamine use variables. The study also had similar limitations as the Jacobs' study, with a relatively small sample size (n=30 in each arm) and use of anti-psychotic medication in all participants in the MAP and schizophrenia groups. Nevertheless, these results are consistent with that of the Jacobs' study, adding strength to the concept of cognitive impairment in MAP that resembles that seen in chronic schizophrenia.

Bouchard and colleagues' study of 172 participants with MAP found that performance on decision making (Iowa Gambling Task) and verbal memory (Hopkin's Verbal Learning Memory) tasks (140) could predict two distinct groups with different cognitive profiles. The study utilised a cluster analysis methodology to identify differences between participants' cognitive performance, aiming to distinguish subgroups of individuals with a primary versus a methamphetamine-induced psychotic disorder on the basis of cognitive functioning. They found that people with poorer decision making and verbal memory were more likely to have negative symptoms of psychosis. This novel finding supports the idea that particular cognitive profiles may correlate with symptom subtypes in MAP and may share a similar neurobiological basis. The inclusion criteria for this study suggested that participants may not have been representative of individuals with MAP, however. All participants in this study had a diagnosis of methamphetamine abuse based on the DSM-IV. Determination of psychosis was based on the presence of current psychotic symptoms, defined by having clinically significant (a score of 4 or more on the Brief Psychiatric Rating Scale) hallucinations or delusional thoughts. This did not include people presenting with suspiciousness or paranoia in the absence of delusional thoughts. Given that the most common psychotic symptom in people with MAP is suspiciousness, and only a minority present with delusional thoughts (90), this definition may have been too narrow. Further, almost all (98.8%) participants had previous psychiatric diagnoses, including 28 (16%) with a diagnosis of schizophrenia and 14 (8%) with bipolar disorder. As such, the cognitive impairments in the study could relate to types of psychosis other than MAP. Similarly, participants also had a high level of other substance use, including regular use of cocaine (24%) and heroin (5%), which could also drive cognitive impairment.

Finally, in a study by Chen and colleagues, people with DSM-IV TR diagnosed methamphetamine abuse or dependence (n=160) were compared to participants with schizophrenia (n=54) and healthy controls (n=67) (139). Participants were abstinent from methamphetamine for at least one

week, confirmed with a negative urine drug screen, and were recruited from detention settings and general and psychiatric inpatient hospital units. The study used a brief 30-minute neuropsychological battery, the Brief Assessment of Cognition in Schizophrenia (BACS). The battery was targeted at cognitive domains recognized as being commonly impaired in people with schizophrenia and being associated with real-world functioning, including verbal and working memory, motor speed, attention and processing speed, verbal fluency, and executive function. The results were controlled for age, gender and level of education. The study found that participants with MA use and no psychosis, and those with brief psychosis (symptoms lasting for less than 1 month following cessation of MA use) had a cognitive profile that did not differ from healthy controls. In contrast, participants with persistent psychotic symptoms (more than 1 month following cessation of MA use) had significantly different results on all BACS domains compared to healthy controls and those with brief psychosis. Furthermore, the persistent psychosis group had similar results on all BACS domains when compared to participants with schizophrenia. In terms of relationship between psychopathology and cognition, the study found that (in methamphetamine users) the negative symptom scores on the BPRS related significantly with verbal memory, working memory, verbal fluency, attention and processing speed and executive function; in contrast, positive symptoms did not correlate significantly with any BACS domain. However, for the schizophrenia group, neither positive nor negative symptoms correlated with any cognitive domains. This study was the first to demonstrate this difference in cognitive profile grouped by the type of MAP. Others have highlighted that the MAP syndrome is heterogeneous in terms of clinical phenotype, and that brief or transient MAP differs from persistent MAP in the types of psychotic symptoms experienced (90, 142-144). Chen's study extends this concept to cognition, further supporting the idea that there are measurable cognitive differences between brief versus persistent MAP. While the clinical and real-world meaningfulness of these cognitive differences is unclear, Chen's findings raise the possibility of the use of cognitive tasks as a marker of psychosis-proneness and persistence(139).

2.3.7 Aspects of cognition impaired in MAP

It is difficult to conduct an exhaustive neuropsychological battery, focusing on all aspects of cognition and social cognition, as this can be time and resource intensive and cause significant participant burden. Consequently, most studies investigating cognition usually focus on a subset of domains hypothesised to be of relevance.

The studies discussed above provide a basis for nominating the key cognitive domains that may be of potential relevance in MAP. Based on studies of individuals with primary psychotic disorders, it appears to be important to study both (i) verbal memory and (ii) social cognition. Secondly, studies of individuals with methamphetamine dependence and MAP have highlighted the need to

examine both social cognition and (iii) impulsivity and reward-based decision-making. These three domains can be investigated in a reliable, practical and feasible manner using computer-based tasks, and so results can potentially be replicated easily.

2.4 KEY GAPS AND LIMITATIONS OF STUDIES OF COGNITION IN MAP

In summary, while previous studies have investigated aspects of cognition and social cognition in methamphetamine-dependent samples, there remain a range of key gaps that are not addressed by existing evidence. Most studies to date have focused on a narrow population with high severity of psychotic symptoms and high severity of methamphetamine dependence (137, 138, 140), meaning that it is not clear whether their findings translate to the majority of methamphetamine users in the community who have less severe psychotic symptoms and methamphetamine use patterns.

Cognition has been proposed as a potentially useful marker to identify individuals with a greater propensity to primary psychosis. As discussed above, given that few non-drug risk factors have been established for MAP, investigating cognition in MAP may present a novel approach to gain insight into a high-risk profile for MAP. The few studies to date focussing on cognition in MAP populations have had methodological limitations that impact on both the internal and external validity of their results. There are no existing studies of social cognition in relation to methamphetamine-associated psychosis, highlighting an important gap in current knowledge. Further, existing studies have not considered the degree and meaningfulness of cognitive impairment in MAP in comparison to healthy controls; or how cognitive impairment may vary based on the presenting symptom profile. Consequently, the nature and extent of cognitive impairment in methamphetamine-related psychosis is unknown.

2.5 SUMMARY: KEY GAPS AND RESEARCH QUESTIONS FOR THIS THESIS

In summary, this thesis aims to investigate two key areas, (i) the role of MA use as a correlate of MAP, and (ii) the association between cognitive and social cognitive markers and psychotic symptoms in MAP. The aims and methods of the individual studies in this thesis are summarized as follows.

2.5.1 THE ROLE OF MA USE AS A CORRELATE OF MAP

The first part of this thesis aims to take a range of methods to explore correlates of MAP in different settings and samples, concluding with a systematic review of the existing evidence for correlates of MAP.

2.5.1.1 INVESTIGATING SOCIODEMOGRAPHIC CORRELATES OF MAP IN PRE-HOSPITAL SAMPLES

The first study will be a cross-sectional study of an acute ambulance dataset, characterising presentations of acute psychosis in methamphetamine-using adults. We hypothesised that there

would be differences in sociodemographic correlates of methamphetamine-related and non-drug related acute psychosis presentations.

2.5.1.2 Investigating clinical correlates of MAP in early-intervention treatment settings

The second study will be a cross-sectional study involving an audit of clinical records of treatment-seekers attending a specialist, early-intervention, outpatient service. We hypothesised that methamphetamine use factors, such as frequency of methamphetamine use, would be correlated with the likelihood of lifetime experiences of psychotic symptoms in this sample.

2.5.1.3 A systematic review of risk factors and correlates of MAP

The third study involves a systematic review of the existing literature to provide a higher level of evidence on the risk factors and correlates of MAP, in order to assist in building a profile of high-risk individuals, and to focus clinical and research efforts.

2.5.2 Association between cognition and psychotic symptoms in MAP

2.5.2.1 Association between cognition and psychotic symptoms in MAP

We aimed to investigate whether markers of cognition and social cognition were related to psychotic symptoms in methamphetamine-using adults. We planned to conduct a cross sectional study of adults using MA regularly, aimed at investigating cognitive correlates of psychosis, whilst accounting for other drug-related or non-drug related predictors of MAP. We hypothesised that markers of cognition and social cognition would be correlated with psychotic symptoms in this sample.

2.5.2.2 Cognition in MAP compared to Healthy controls

Previous critiques of studies of cognition in methamphetamine dependence highlighted the need for cognitive performance in subjects to be compared against relevant controls. Here, we aimed to compare cognitive and social cognitive performance in methamphetamine-using adults (with and without psychotic symptoms) against healthy controls. We hypothesised that cognition would be impaired most in methamphetamine-using adults with psychotic symptoms, and to a lower degree in methamphetamine-using adults without psychotic symptoms, in comparison to healthy controls.

2.5.2.3 Variation in cognition in MAP with positive psychotic symptom profile

Finally, in the context of evidence that presenting syndromes in MAP are heterogenous, we aimed to conduct further analyses to identify whether there was any variation in cognitive profiles in relation to predominant positive psychotic symptom profiles.

In conclusion, the different studies in this thesis aimed to develop a comprehensive understanding of correlates of psychotic symptoms in methamphetamine-using adults, towards

guiding key future clinical and research directions in this area.

Chapter 3

Expanded Methodology

The aim of this thesis is to inform a better understanding of the predictors and correlates of MAP, with a focus on cognitive factors. This was investigated using mixed-method methodology.

Below is a summary of the studies in this thesis with an overview of the aims, design, measures and analyses undertaken in each study (See Table).

Table: Summary of Studies

Chapter	Title	Aim/s	Design	Sample size	Measures	Analyses
4	The role of MA in psychosis-related ambulance presentations	To investigate sociodemographic correlates of acute presentations of MAP in comparison with primary psychosis	Cross-sectional study, based on large Victorian ambulance dataset 2012-2014	N=8811 (N=627 MAP, N=8184 non-drug related psychosis)	Factors related to attendance (location, duration, transport to hospital); and factors related to presentation (self-harm, previous psychosis history)	Descriptive statistics for each presentation type (MAP; non-drug related) Chi-square tests for between group comparisons
5	Key differences in treatment-seeking stimulant users attending a specialised treatment service: a means of early intervention?	To examine sociodemographic and clinical correlates of MAP in a specialised treatment-seeking stimulant use population	Cross-sectional audit of case files	N= 175	Sociodemographic factors, methamphetamine use factors, mental health comorbidity	Descriptive statistics characterizing study sample Univariate logistic regression for relationship between factors and mental health harms, psychosis
6	A Systematic Review of Risk Factors for MAP	To systematically review and synthesise the literature on risk factors and correlates of MAP	Systematic review	20 studies N=5476	Correlates including sociodemographic, methamphetamine and other drug use factors, psychiatric comorbidity, trauma, family history	Qualitative synthesis

					Individual study quality (modified NewcastleOttawaScale);Overall qualityofevidence(GRADEcriteria)	
7	Cognitive and social cognitive correlates of MAP	To investigate cognitive and social cognitive correlates of MAP To investigate how cognitive correlates of psychotic symptoms in MAP differ based on presenting symptom profile	Cross-sectional study	N=103 MA use	Exclusion of schizophrenia or bipolar disorder (SCID I/P) Sociodemographic (age, gender, years of education) MA use patterns (questionnaire, TLFB, SDS) General cognitive functioning (IQ WASI-II) Past month positive psychotic symptoms (BPRS) included (i) suspiciousness, (ii) hallucinations and (iii) unusual thought content Neuropsychological battery (Verbal memory HVLT-R, Delay Discounting DDT, Decision Making IGT, Facial Emotion Recognition EFT)	(i) Descriptive statistics to characterize sample (ii) Associations between past month psychotic symptoms and methamphetamine use variables, and demographic, clinical and cognitive measures to identify confounders (using Spearman correlations and Mann-Whitney U tests) (iii) Relationship between pastmonth positive psychotic symptoms and cognitive correlates adjusting for confounders, using multiple regression (truncated negative binomial regression) (iv) Relationship between each positive psychotic symptom domain

						score and cognitive correlates, using multivariate regression, with unadjusted and adjusted measures of association
8	Facial emotion recognition in MAP compared to healthy controls	To investigate differences in facial emotionrecognition inMAuserswithand without clinically significant psychotic symptoms, in comparison with healthy controls	Cross-sectional study	MNPN=73 MAPN=30 HC N=48	Measures as above -Past month positive psychotic symptoms defined as only 'clinically significant' symptoms(atleast 4 or more on any BPRS positive symptom item)	(i) Descriptive statistics to characterizesample,anddifferences between sample and healthy controls (ii) Regressionanalysistoexamine associations between cognitive correlatesandMAP,withreference to healthycontrols;withadjustment for

						potentialconfounders

SCIDI/PStructuredClinicalInterviewforDSM-IV(30)WASI-IIWeschlerAbbreviatedScaleofIntelligence-SecondEdition(146)TLFBTimelineFollowback(147)SDSSeverity ofDependence Scale(148)BPRSBriefPsychiatricRatingScale(40)DDTDelayDiscountingTask(149)IGTIowa GamblingTaskEFT(150)EkmanFacesTask(151)

3.1. THE ROLE OF METHAMPHETAMINES IN PSYCHOSIS-RELATED AMBULANCE PRESENTATIONS

3.1.1. AIMS

Previous studies have highlighted the similarities between acute presentations of MAP and schizophrenia. Presentations of MAP in acute health settings can comprise a diagnostic dilemma for frontline clinicians. This study sought to investigate any demographic correlates that could distinguish acute presentations of MAP from primary psychosis.

3.1.2. STUDY DESIGN

This was a cross-sectional study examining illicit drug involvement in Victorian ambulance attendances where patients presented with psychosis symptoms between January 2012 and August 2014 (n=8811).

3.1.3. PROCEDURE

The study was based on data collected for the "*Ambo Project*", which examines alcohol and other drug-related events attended by ambulance paramedics across metropolitan and regional Victoria, with the aim of monitoring drug-related trends and harms. It is a collaborative project between Turning Point and Ambulance Victoria, funded by the Victorian Department of Health and Human Services, and the Commonwealth Department of Health and Ageing. Data in the "*Ambo Project*" database was available from 1998 onwards for metropolitan Melbourne; from mid-2011 onwards for regional and metropolitan Victoria; and from 2012 onwards to include monitoring of drug-related self-harm and mental health-related presentations. Patient care records completed by paramedics at the point-of-care are parsed into an electronic database, with specifically trained research staff subsequently extracting and manually coding individual presentations for a range of alcohol and other drug (AOD) and mental health variables. Auditing and formal quality control procedures further support the correct identification of substances involved in a presentation. Further details regarding the methods used in the "Ambo Project" are available elsewhere (152, 153).

For this study, data were collected from the "*Ambo Project*" database for the period Jan 2012-Aug 2014. This period was chosen as the most recent period for which a complete set of data were available for both metropolitan and regional jurisdictions in Victoria for drug-related presentations and associated mental health harms.

All attendances for psychosis, both primary (n=8184) and drug-related (n=627), were examined to identify the drug associated with the greatest burden of harm related to psychosis. Secondly, presentations for methamphetamine-associated psychosis were compared to non-drug related

psychosis, to examine differences in characteristics relating to the attendance and to the presentation.

3.1.4. MEASURES

The following data were collected.

Demographic characteristics: Age, gender

Details regarding attendance: Length of attendance, transport to hospital, police co-attendance, location of attendance (indoor versus outdoor/public, metropolitan versus regional)

Details regarding presentation: Features of presentation, including presence of self-harm, and self-reported past history of psychosis

3.1.5. STATISTICAL ANALYSIS

Descriptive statistics were generated for all non-drug related and methamphetamine-related psychosis attendances. Subsequently, the two groups (MAP and non-drug related psychoses) were compared on a range of variables, using Pearson chi square tests for categorical data and independent t tests for continuous data. All tests were conducted with two-tailed tests of significance, with a significance level of $p<0.05$. Statistical analysis was conducted using Stata 15 (Statacorp LP, College Station,TX, USA).

3.2. KEY DIFFERENCES IN TREATMENT-SEEKING STIMULANT USERS ATTENDING A SPECIALISED TREATMENT SERVICE: A MEANS OF EARLY INTERVENTION?

3.2.1. AIMS

While previous studies had identified that methamphetamine use factors played a key role in increasing risk for MAP, the role of sociodemographic and clinical variables, such as previous psychiatric history, was less clear. In addition, previous studies had largely been conducted in severely dependent populations recruited from detention or rehabilitation settings. In this study, we sought to investigate clinical correlates of MAP (including drug use factors) in a specialised outpatient AOD treatment setting.

3.2.2. STUDY DESIGN

We utilised a cross-sectional study design to examine the prevalence of MAP, and associations between psychosis and MA use patterns.

The *Access Point* clinic was a stimulant-specific outpatient treatment clinic that delivered multidisciplinary care to over 200 adults in metropolitan Melbourne, Australia over a period of six years (2008-2014). The clinic was set up to address the needs of a stimulant-specific cohort

of treatment-seeking adults, with the hope of tailoring care to this population to improve engagement and treatment retention. Patients could self-refer to the clinic or be referred by a health professional. *Access Point* was the only stimulant-specific treatment service in the state of Victoria during its period of operation.

The service sat alongside mainstream AOD services, but was unique in having its own intake system, allowing individuals to access support directly, in person or via a dedicated telephone service or website. It aimed to deliver medically-supported psychological counselling treatment to individuals seeking help for stimulant use disorders, and was staffed by experienced professionals, including a clinical psychologist, social worker, nurse, and psychiatrist and addiction medicine specialist. Staff were specifically trained in the screening, assessment and treatment needs of stimulant users, and routinely assessed for mental health harms associated with methamphetamine use such as methamphetamine-associated psychosis.

3.2.3. Procedure

Firstly, the study involved a retrospective audit of the clinical records of adults (aged 18-65) who sought treatment at the Access Point clinic in the six-year period 2008-2014. Client records were eligible for inclusion if the client had completed an assessment (n=175). Incomplete assessments were not included. The clinical record contained information routinely gathered during the assessment interview, with most assessments taking between 1-2 sessions. The following information was collected using a structured interview and intake tool, based on patient self-report, and information reported by families or referrers. Three clinicians at the service conducted the audit using a structured electronic data collection tool. The auditing clinicians met regularly over the course of the study to ensure consistency in data collection methods.

Secondly, the socio-demographic and substance use characteristics of this sample were compared to three other samples from other studies conducted in Australia over this period: a sample of adults seeking residential detoxification treatment for methamphetamine use and a sample of adults seeking residential rehabilitation treatment for methamphetamine use (both in the same study)(154), and a community-based sample of non-treatment seeking methamphetamine using adults(155).

3.2.4. Measures

For the clinical audit, the following data were gathered using a structured electronic data collection tool.

Demographic Information: Sociodemographic data including age, gender, sexual orientation, accommodation and primary source of income.

Methamphetamine use and other drug use: Primary drug of concern, primary route of use (intravenous injecting, inhalation/smoking, snorting, or other), average amount of drug used per occasion (in grams), frequency of use, and estimated duration of episode use. Other current drug use and dependence, previous history of drug use and dependence

Psychotic symptoms: A self-reported history of past experiences of psychotic symptoms (including paranoia, auditory or visual hallucinations), both whilst intoxicated, and whilst not drug-affected.

Other mental health problems: A self-reported history of current and previous mental health history, including previous mental health diagnoses, and previous suicide attempts.

3.2.5. Statistical Analysis

Descriptive statistics were calculated to characterize the study sample. Univariate logistic regression analysis was conducted to investigate the associations between socio-demographic, health and substance use variables and methamphetamine associated mental health harms, including psychosis. All data analysis was undertaken using IBM SPSS 22.

3.3 A Systematic Review of Risk Factors for Methamphetamine-Associated Psychosis

3.3.1. Aims

While there were several previous studies examining correlates of MAP, results of original studies were contradictory, and previous reviews had not been systematic in methodology. Consequently, there was no consolidated consensus in the literature on what risk factors were the most consistent correlates of MAP. This study aimed to review and synthesize the literature on risk factors and correlates for MAP.

3.3.2. Study Design

The detailed methodology for this study is presented within the paper in Chapter 4, and summarized here.

The systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and MetaAnalyses (PRISMA) guidelines. Details of the systematic review protocol were registered on PROSPERO International Prospective Register of Systematic Reviews (Registration: 42016052223) prior to data extraction.

3.3.3. PROCEDURE

3.3.3.1. STUDY ELIGIBILITY

Studies were included if they met the following criteria: (a) Participants were adult (>17yo) humans with current use (within the last 12 months) of illicit methamphetamine or amphetamine (MA); (b) Participants using MA with current or lifetime psychosis symptoms (referred to as MAP) were compared with those using MA without psychosis symptoms (MNP), where psychosis was measured using a validated instrument or structured interview; and (c) individuals identifying MA as their primary drug were identified and analysed separately from those citing other substances as their primary drug.

3.3.3.2. SEARCH STRATEGY

Electronic searches were performed on the following databases: Medline (OVID), PsycINFO and EMBASE databases, from the earliest available dates to 8 December 2016. The search strategy combined three concepts: methamphetamine or amphetamine, psychosis and risk factors. Search terms for methamphetamine included: METHAMPHETAMINE, AMPHETAMINE, METHYL-AMPHETAMINE, METHAMPHETAMINE, METHAMFETAMINE; search terms for psychosis included DRUG-INDUCED PSYCHOSIS, SUBSTANCE-INDUCED PSYCHOSIS, PSYCHOSIS, PSYCHOSES, SCHIZOPHRENIA, SCHIZO-AFFECTIVE; and, search terms for risk factors included RISK FACTORS, VULNERABILITY FACTORS, PREDISPOSING FACTORS. In databases where Medical Subject Headings (MeSH) terms were available, they were exploded and combined. No language restrictions were applied to the search.
The reference lists of previous reviews (21, 156) and articles identified in the main search were also screened for citations not identified in the main search. As this supplementary search identified five further citations, we elected to perform an additional search using Google Scholar to identify articles that had cited those articles identified in the main search, in an effort to avoid missing any potentially relevant articles. The review protocol was updated to reflect this further search. Screening of titles, abstracts and subsequently full texts was performed independently by two authors. Any disagreements regarding study inclusion were resolved by discussion.

3.3.3.3. STUDY DESIGN AND DATA EXTRACTION

Single case reports, literature reviews and studies in animals were excluded. The following data were extracted from studies: study country, setting and design; participant demographic and clinical details; sample size; measure/s used; and measures of association between risk factors and psychosis outcomes. Studies were categorised based on whether psychosis was assessed using a current or lifetime measure. Risk factors were classified according to the following

categories: (i) sociodemographic factors (including age, gender, employment, educational status, housing status, socioeconomic status) (ii) methamphetamine use patterns (including measures of methamphetamine use, amount, frequency, duration of use, age of onset of use, route of use) (iii) other drug use (iv) psychiatric co-morbidity (including current and previous psychiatric illness and personality disorders) and (v) family history (of psychotic or other psychiatric illness) and (vi) history of trauma.

An electronic data extraction tool was piloted on one study, refined, and subsequently used by two authors to independently extract data from each included study. Multiple studies conducted on the same population were combined, and data were then extracted together as one study. Where there were uncertainties about the data in studies, or where methamphetamine-specific outcomes were not reported, we contacted authors for further clarification and re-analysis of original data.

3.3.3.4. Quality Assessment

As there is no accepted gold standard instrument for assessing quality of observational studies, a modified version of the Newcastle-Ottawa Scale (157) was developed specifically for use in this review. The studies were scored on the following domains: (a) representativeness of the cohort (out of 3), (b) assessment of risk factor (out of 3), (c) demonstration that psychosis was not present at the start of the study (out of 2), (d) comparability of the two groups and controls for confounding (out of 2) and (e) assessment of the outcome of psychosis (out of 3), with a final quality score out of 13. SA and JF independently assessed the quality of included studies, with final scores derived by consensus between those two authors. Based on evidence across studies, outcome level quality for each predictor was assessed by consensus between two authors with reference to the GRADE criteria, considering study design, study quality, consistency and directness for each predictor (158). Inconsistency in evidence was determined by consideration of qualitative study heterogeneity, variation in effect sizes, study populations and outcome definition with reference to the Cochrane guidelines (159).

3.3.3.5. Study Synthesis

Meta-analysis was planned for correlates reported consistently across 3 or more studies, where heterogeneity was acceptable. However, lack of consistency in reporting prevented meta-analysis for any correlates, therefore synthesis of results was by narrative review.

3.4 Cognitive correlates of Methamphetamine-Associated Psychosis

3.4.1. Study Design

This study aimed to investigate novel cognitive correlates of MAP. It involved a cross-sectional study of adults who use methamphetamine regularly, examining the relationship between methamphetamine use, psychosis, and cognition.

As discussed in Chapter 2, a number of factors were considered to be relevant in understanding the association between cognition, MA and MAP as they may be potential confounding factors, or intervening variables. As identified in a recent meta-analysis of cognition and social cognition in methamphetamine dependence, relevant potential confounding factors that have been adjusted for in previous studies have included age, gender, general cognitive functioning or IQ, and severity of drug use (129). These factors were identified as potential moderators or confounders a priori, and we sought to measure and statistically adjust for them in the analysis in this study.

3.4.2. Procedure

3.4.2.1. Sample selection, inclusion & exclusion criteria

The target population for this study was adults who were using methamphetamine regularly. The study also aimed to maximise the generalizability and external validity of findings, so the results could be easily translated to real-world settings. Consequently, we adopted a pragmatic approach to the sampling strategy.

The definition of regular use of methamphetamine was broad in order to capture a spread of methamphetamine use patterns and doses, and was based on the inclusion criteria of previous studies of MAP (36, 48, 49, 160, 161) with a minimum level of use defined as at least monthly in the past six months.

Polydrug use patterns are typical in the Australian population. Polydrug use has been described as “nearly universal” (155) in both community-based (48, 155) and treatment-seeking (36, 42) samples of people who use methamphetamine in Australia, with use of nicotine, cannabis and alcohol most commonly reported(3). Thus, while it would be ideal to recruit participants who only use methamphetamine in order to exclude the potential impact of other drug use on outcomes, previous studies have demonstrated that this is not typical of people who use drugs in Australia(154), and this would pose challenges both for recruitment and for the generalisability of the results. Consequently, the study included participants who were

dependent on the most prevalent drugs (nicotine, cannabis and alcohol) but excluded participants dependent on any illicit drugs other than methamphetamine.

The study also incorporated a range of neuropsychological tasks examining cognitive performance, so exclusion criteria for the study included the presence of conditions that were likely to impact on cognition, including (i) neurological illness (including HIV, epilepsy, multiple sclerosis) (ii) intellectual disability, defined as an IQ of <70 and (iii) traumatic brain injury.

In summary, the following inclusion and exclusion criteria were used:

Participants were (i) adults aged 18-55 years old who (ii) used methamphetamine at least monthly in the past six months, and identified methamphetamine as their primary drug of concern and (ii) were not dependent on drugs other than methamphetamine, nicotine, cannabis or alcohol, who (iii) did not have a pre-existing primary psychotic disorder (defined as schizophrenia, schizoaffective disorder or bipolar disorder), as assessed by the SCID I/P for DSM-IV or (iv) any active mental health illness currently requiring psychotropic medication. Exclusion criteria were the presence of (i) a self-reported history of a traumatic brain injury, central nervous system disorder, (including epilepsy, multiple sclerosis, HIV) or (ii) intellectual disability, as defined by an IQ <80.

3.4.2.2. RECRUITMENT & SETTING

Participants were recruited from both the community (non-treatment-seeking) and treatment services. Previous studies have demonstrated that the level of methamphetamine use and the prevalence of psychotic symptoms vary between treatment-seeking and non-treatment seeking samples of methamphetamine-using adults (10). We therefore aimed to recruit participants from both treatment services and from the community to gather a representative sample of methamphetamine use patterns, doses and prevalence of psychosis.

Participants were recruited between April 2015 to February 2017. Participants from the community were recruited using methods used by previous investigators, including advertisements in free-press and music magazines (49, 155), and information flyers in needle syringe exchange programmes (160). Participants from treatment services were recruited from both public and private residential and outpatient treatment services, with clinicians identifying individuals from their caseload who they thought may be suitable for the study, and researchers then contacting participants directly to conduct further screening for eligibility.

3.4.2.3. PROCEDURES

The study procedures were consistent with the National Health & Medical Research Council National Statement on Ethical Conduct in Human Research and received Human Research Ethics Committee approval from Monash University (CF15/450 - 2015000222) and Eastern Health (E52/1213).

A face-to-face 1.5 hour interview was carried out by a researcher at a mutually convenient time and quiet location. Participants were requested to abstain from using alcohol or any drugs on the day of the assessment. Participants who appeared to be intoxicated or reported substance use on the day of the assessment, had the assessment re-scheduled to a subsequent day. Those who were eligible to participate completed informed consent and were reimbursed AU$30 in a supermarket voucher for their time and expenses.

The Structured Clinical Interview for DSM-IV TR (SCID-I/P)(30) modules for substance dependence, schizophrenia and bipolar disorder were used to diagnose a lifetime history of DSM-IV diagnoses of schizophrenia or bipolar disorder, and evaluate current substance dependence diagnoses.

3.4.2.4. MEASURES

The measures utilized in this study are summarized below.

Table 5: Measures in cross-sectional study of cognition in methamphetamine-using adults

	Data	Measure	Dependent Variable
Sociodemographic Data	Age, gender, employment status, years of education	Structured self-report questionnaire	Age, gender, employment status, years of education
Substance use	Frequency of methamphetamine use in past month	Timeline Followback method (TLFB)(147)	Number of days of use
	Severity of methamphetamine dependence	Severity of Dependence scale (SDS)(148)	SDS Total score
	Methamphetamine use patterns (route, amount, age of first use, years of use)	Structured self-report questionnaire	Route, amount, age of first use, years of use
	Other drug dependence	Structured Clinical Interview for DSM-IV (SCID I/P)(30)	DSM-IV diagnoses for cannabis and alcohol dependence
Psychotic symptoms	Past month positive psychotic symptoms	Brief Psychiatric Rating Scale (BPRS)(80)	BPRS Total positive symptom score BPRS symptom score for each positive symptom item
Cognitive battery	General cognitive functioning –IQ	Weschler Abbreviated Scale of Intelligence- Second Edition (WASI-II) Vocabulary and Matrix Reasoning subscales (146)	Estimated full scale IQ
	Verbal memory and learning	Hopkin's Verbal Learning Test- Revised (162)	HVLT-R delayed recall score
	Decision Making- Impulsive Choice Delay Discounting	Delay Discounting Task (149)	DDT k score

	Decision Making- Balancing risk and reward Iowa Gambling Task	Iowa Gambling Task (IGT) (150)	IGT net score
	Social cognition- Facial Emotion Recognition Ekman Faces Task	Ekman Faces Test (151)	Total number of correct identification- EFT total score Number of correct identifications for each emotion

3.4.2.5. SUBSTANCE USE

Frequency: The frequency of methamphetamine use in the past month was assessed using the Timeline Followback (TLFB)(163). This is a structured method of estimating retrospective drug use, using a calendar and other memory aids (e.g. important dates, birthdays, public holidays as anchor points) to enhance the reliability of self-reported frequency of drug use. It has been demonstrated to have 88% sensitivity, 96% specificity, a 95% hit-rate and 0.77 test-retest agreement, for the use of amphetamines in the past 30 days(147).

Severity of Dependence (SDS): The severity of dependence on methamphetamine, cannabis and alcohol was measured using the Severity of Dependence Scale (148). This is a five-item measure with responses rated on a four-point Likert scale, resulting in scores ranging from 0-15 (low severity to high severity of dependence), with high validity and reliability in drug-dependent populations(164).

Other methamphetamine use variables: A structured questionnaire was used to assess self-reported (i) main route of methamphetamine use (ii) amount of methamphetamine use per occasion (iii) age of first methamphetamine use and (iv)years of methamphetamine use.

3.4.2.6. PSYCHOTIC SYMPTOMS

Brief Psychiatric Rating Scale: The presence of past month psychotic symptoms was assessed using the Brief Psychiatric Rating Scale (BPRS)(165). This is a dimensional measure of psychosis, based on a structured interview conducted by a trained interviewer. The BPRS is a widely-used measure of psychotic symptoms and has been used in several previous studies of methamphetamine-dependent populations (42, 49, 141, 160, 166). It has a high inter-rater reliability, as reported in original studies (r= 0.67-0.88)(40) .
The expanded version of the measure consists of 24 items, 14 of which are rated based on the participant's self-report, and 10 of which are based on the interviewer's assessment of observed behaviour and speech(40). Each item incorporates a judgement of the symptom frequency, severity and level of impact on function. Interviewers rate each item between 1-7 on the basis of severity, with 1 being "not present", to 7 being "extremely severe". Ratings are made in reference to structured anchor points.The dependent variables used in this study included the total score of the three positive symptom items of suspiciousness, hallucinations and unusual thought content (ranging from 3-21) and the three negative symptom items of blunted affect, emotional withdrawal and motor retardation (ranging from 3-21)(167). All research interviews were conducted by postgraduate researchers with clinical experience, who had completed training in the BPRS.

3.4.2.7. NEUROPSYCHOLOGICAL BATTERY

The measures chosen for the following battery were based on the literature review of cognition in methamphetamine use and MAP, as outlined in Chapter 2. In summary, the neuropsychological test battery targeted cognitive domains associated with stimulant use(141) (168) (169) (130) (170) (171), and impairments in emotion perception associated with psychotic disorders (172) (173).

The tasks were administered in a set order and nested within the structured interview, interspersed with the symptom measures above, in order to reduce participant fatigue.

(1) *General Intellectual Functioning*

Wechsler Abbreviated Scale of Intelligence—Second Edition (WASI-II): This assessment of current intellectual functioning comprises of four tasks, measuring performance IQ (visuospatial abilities) and verbal IQ (language comprehension and expression)(146). In this study, a briefer version was used to generate an estimate of IQ, by utilizing the Vocabulary and Matrix Reasoning tasks. This approach has been previously demonstrated to be more expedient, whilst maintaining validity and reliability of IQ estimation(146).

(2) *Impulsive Choice in Decision-Making- Delay Discounting (DDT)(149)*

Delay discounting refers to the extent to which an individual prefers smaller, immediate rewards versus larger, delayed rewards, and is a measure of impulsive choice in decision-making(149). As delay discounting increases, people become more likely to choose proximal rewards, and to make decisions that can be considered as impulsive(149).

A 27-item multiple-choice paper-based version of this task was used in this study, based on the Kirby Monetary Choice Questionnaire(149), demonstrated to be highly valid and reliable. The main dependent variable for this task was calculated as the k score, based on methods detailed by Kirby and colleagues, with the k value providing an estimate of how rapidly monetary value is degraded for each individual, with higher k scores indicating higher levels of impulsivity(149).

(3) *Evaluating Reward and Risk in Decision-Making- the Iowa Gambling Task (IGT)(150)*

This task was originally developed to assess decision-making in individuals with damage to the orbitofrontal cortex(150), and has been used in diverse populations (including people with obsessive compulsive disorder, addiction, pathological gambling, attention deficit hyperactivity disorder and psychosis) to measure 'real-world' decision-making in

laboratory-based settings (174). The IGT is a computerized task that assesses several aspects of decision- making, including risk, uncertainty, and evaluation of reward. The IGT involves four decks or cards (decks A, B, C and D), and participants are instructed to win as much hypothetical amounts of money as possible by picking one card at a time from each of the four decks in any order, until the computer instructs them to stop (after the selection of the 100th card). Each time an individual selects a card, a specified amount of money is awarded. However, interspersed among these rewards, there are probabilistic punishments, resulting in monetary losses of different amounts. Two of the decks of cards, decks A and B, produce higher immediate gains, but eventually these two decks will take more money than they give, and so are considered to be disadvantageous. The other two decks, decks C and D, are considered advantageous, as they result in smaller immediate gains, but will generate greater amounts of money than they take in the long run. The main outcome variable generated from this task is the difference between the number of advantageous and disadvantageous deck choices [(C+D) (A+B)] on each of the five blocks of 20 trials of the task.

(4) *Verbal Memory and Learning: Hopkins Verbal Learning Test- Revised (HVLT-R)(162)*
This is a paper-based task, examining immediate and delayed verbal recall and recognition. Participants are read a list of 12 words, and asked to immediately recall as many as can, with the procedure repeated two times (for a total of three learning trials). Following a 20–25 minutes delay, participants are asked to recall the word list without any cues (delayed recall). They are subsequently read a list of 24 words, and have to identify the 12 words from the original list (recognition). The dependent variable used in this study HVLT-R was the number of words remembered on the delayed recall subtest, ranging from 0-12.

(5) *Social Cognition- Facial Emotion Recognition: Ekman's Faces Test (151)*
This is a computerised task that assesses recognition of facial emotional expression and has been widely used in studies of psychosis(175) and substance dependence(176) . A series of 60 faces portraying basic emotions are presented, using stimuli from the Facial Expressions of Emotion: Stimuli and Tests (FEEST)(151). Faces were presented as static monochromatic images, with an example presented below (see figure below). Faces depicted the following six emotions, anger, fear, disgust, happiness, sadness, surprise;

with 10 static faces for each of the 6 emotions. The dependent variables for this task were the total number of correct identifications (ranging 0-60).

Figure 3: Example of stimuli for Ekman Faces Task (177)

3.4.3. STATISTICAL ANALYSIS

3.4.3.1. DATA PREPARATION PROCEDURES

Data was collected using both pen-and-paper and computerized tasks. Tasks were manually scored simultaneously with data collection. Data was manually entered into a central computerized database as the study progressed. Following the completion of data collection, data cleaning was undertaken, and the database was examined for missing data, errors and outliers.

A listwise deletion approach was undertaken to addressing missing data. At a minimum, participants were required to have valid data for the key dependent variables in the study (i) psychosis symptoms, (ii) cognition and (iii) facial emotion recognition. Participants with missing data for any of these measures were dropped from the dataset (n=8).

The remaining data was reviewed for any potential errors or outliers, utilizing scatter plots for each key dependent variable. Participants that were clear outliers on cognition and facial emotion recognition scores (n=2) were reviewed and discussed with the research team, with potential reasons for low scores on these tasks considered (e.g. substance intoxication, participant fatigue). Given the low number of cases with outlying data, the decision was made to remove these cases from the dataset.

3.4.3.2. DISTRIBUTIONS

Descriptive statistics were calculated for each variable. Histograms were used to characterize the distribution for each variable. Key dependent variables (scores on cognitive tasks (HVLT-R, DDT k score, IGT net score) and facial emotion recognition (EFT total score) were identified as having non-normal distributions.

The positive psychotic symptom score was an over-dispersed count variable, with a minimum score of 3, and a greater variance than mean (variance 9.5 > mean 5.95). Given this distribution, statistical support was sought to identify the most appropriate multiple regression approach for the relationship between psychotic symptoms and cognition, with truncated negative binomial regression (lower limit of 3) identified as having the best fit (178).

3.4.3.3. ANALYSIS

Firstly, we sought to identify confounding variables for the relationship between (i) cognition and psychotic symptoms and (ii) cognition and methamphetamine use. Associations between (i) past month psychotic symptoms (total BPRS positive symptom score) and (ii) methamphetamine use variables (severity of dependence, frequency of use and age of onset of use), and demographic, clinical and cognitive measures were assessed using non-parametric measures of association (Spearman correlations and Mann-Whitney U tests).

We then performed a multiple regression analysis using the total positive symptoms score as the outcome measure, and total emotion recognition score as the predictor variable, adjusting for the following confounding variables: age, gender, full scale IQ, and severity of methamphetamine dependence, using truncated negative binomial regression.

All data analyses were conducted using Stata Version 15.0 (Statacorp LP, College Station,TX, USA), with a statistical significance level of $p < 0.05$ and 2-tailed tests of significance.

3.5. UNDERSTANDING THE MEANINGFULNESS OF COGNITIVE CORRELATES OF MAP

3.5.1. STUDY DESIGN

This study was aimed at understanding how the cognitive correlates identified in the previous study differed in MA users with past month clinically significant psychotic symptoms, compared to those without psychotic symptoms, in reference to healthy control participants. This study utilized data from the previous cross-sectional study, with further analyses conducted on a group of healthy controls subjects.

3.5.2. PROCEDURES

Procedures for recruitment of the methamphetamine use population were as described in the study above.

Healthy control participants with no current substance dependence were recruited from the same catchment as cases. Healthy controls were considered eligible for the study if they meet the following criteria: (1) aged between 18 and 50 years old; (2) no current illicit drug use; (3) use of any illicit drug less than 10 times during lifetime; (4) do not meet DSM criteria for current Axis I disorders requiring ongoing psychotropic medication; (5) absence of history of traumatic brain injury involving loss of consciousness of more than 30 minutes or medical conditions impacting the central nervous system; (6) an IQ>80 measured using the Wechsler Abbreviated Scale of Intelligence (WASI). Healthy controls were recruited through (1) flyers posted in local community and leisure centres; (2) advertisements in local and state newspapers; and (3) snowballing among healthy control participants′ acquaintances. There were no statistically significant differences in age, gender or IQ in healthy control participants, compared to the methamphetamine-using group.

Participants were divided into three groups, healthy controls (HC, n=48), people with methamphetamine use and no past month clinically significant positive psychotic symptoms (MNP, n=73), and people with methamphetamine use *and* past month clinically significant positive psychotic symptoms (MAP, n=30).

3.5.3. MEASURES

The measures used in this study were as described in the study above. For this study, a threshold for past-month psychotic symptoms was defined as a score of 4 or above on any positive psychotic symptom item on the BPRS, based on previous studies(161). Healthy control

participants completed the neuropsychological battery, but did not complete questionnaires relating to current drug use, nor current psychotic symptoms.

3.5.4. Statistical Analysis

Firstly, demographic data was compared across all three groups (MAP, MNP, HC) using chi-squares and one-way ANOVAs to identify any significant between-group differences and potential confounders. Methamphetamine and drug use variables were compared across MAP and MNP groups using chi-squares. Secondly, multiple regression was used to compare correlation coefficients between cognitive variables and psychotic symptom group membership (MAP, MNP) with reference to healthy controls (HC). An unadjusted and adjusted (age and any other potential confounders) model was presented. All tests were two-tailed with statistical significance set at $p < 0.05$. Statistical analyses were performed using Stata 15 (Statacorp LP, College Station, TX, USA).

3.6. Understanding associations between cognitive correlates of MAP and symptom subtypes

3.6.1. Study Design

Given that there is significant heterogeneity in the presenting syndrome of MAP, this study was aimed at investigating whether cognitive correlates of MAP identified in the preceding studies (5-6) differed based on the presenting psychotic symptom profile. This study utilized data from the previous cross-sectional study, with specific sub-analyses based on psychotic symptom domains.

3.6.2. Procedures

Procedures for recruitment of the methamphetamine use participants were as described in the study (5) above.

3.6.3. Measures

The measures used in this study were as described in the study above. For this study, the psychosis outcome variable was the individual symptom score for each positive psychotic symptom domain on the Brief Psychiatric Rating Scale, namely (i) suspiciousness, (ii) hallucinations and (iii) unusual thought content.

3.6.4. Statistical Analysis

We investigated the relationship between positive psychotic symptom domains and cognitive correlates using multivariate regression, adjusting for potential confounders. A truncated negative binomial regression method was used to model psychotic symptoms, as an overdispersed count outcome (179), reporting the incidence rate ratio (IRR) and p values with a significance level of 0.05. All analyses were performed using Stata 15 (Statacorp LP, College Station,TX, USA).

Chapter 4

Study 1: Demographic correlates of acute MAP

4.1 PREAMBLE

The first research question investigated in this thesis is whether there are sociodemographic factors that differ between acute presentations of MAP and primary psychosis. We chose to investigate this within a dataset of acute ambulance presentations, and the results of this study are outlined in the following manuscript.

Declaration for Thesis Chapter 4

Monash University

Declaration by candidate

In the case of Chapter 4, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation, data analysis, manuscript preparation	60%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution
Caroline X. Gao	Data analysis and support with statistical methods
Belinda Lloyd	Access to dataset and support with statistical methods
Karen Smith	Access to dataset
Prof Dan Lubman	Supervision and review of manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 02/09/18
Main Supervisor's Signature	[redacted]	**Date** 02/09/18

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

ANZJP

Australian & New Zealand Journal of Psychiatry
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Letter

The role of methamphetamines in psychosis-related ambulance presentations

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DOI: 10.1177/0004867415585323

To the Editor,

Sara et al.'s (2015) meta-analysis found a high rate of stimulant use disorders among people with psychosis, suggesting that stimulants are likely to make a significant contribution to the overall burden of psychosis. However, as Sara et al. (2015) excluded studies that primarily focussed on samples of individuals with substance-induced psychosis, the contribution of stimulants to the overall burden of psychosis is likely to be greater, given consistent evidence that regular stimulant use can increase the risk of experiencing psychosis in a dose-dependent manner (McKetin et al., 2013). Despite growing concerns regarding increasing rates of stimulant use and related harms (especially methamphetamine [MA]) in Australia, as yet, few studies have quantified the impact of stimulant use on psychosis presentations to acute health systems.

We examined illicit drug involvement in Victorian ambulance attendances where patients presented with psychosis symptoms between January 2012 and August 2014 to characterise the acute harms associated with MA-related psychosis presentations. Data were extracted from the *Ambo Project* database.[1] Analysis of all ambulance attendances for psychosis over this period showed that stimulant drugs were more likely to be implicated in presentations of psychosis in comparison with all other illicit drugs combined. MA was the drug most commonly associated with drug-related psychosis, comprising 6.1% of all ambulance attendances for psychosis, and 93% of all stimulant-related psychosis presentations; 13.4% of MA-related psychosis presentations also involved cannabis use, a common co-morbidity highlighted by Sara et al. (2015).

Further analysis was undertaken to compare MA-related psychosis presentations to those where no drug use was reported (Table 1). A significantly higher proportion of MA-related psychosis presentations involved younger

Table 1. Comparison of characteristics of Victorian ambulance presentations for psychosis symptoms by drug use, January 2012–August 2014.

	MA-related ($N = 627$)	Non-drug-related ($N = 8184$)	χ^2
Median length (mins) of attendances[a] (interquartile range)	77 (59–98)	75 (56–98)	1.99
Median age (interquartile range)	28 (23–33)	39 (28–51)	366.92***
Male (%)	419 (66.9%)	4180 (51.1%)	58.28***
Transport to hospital (%)	576 (93.4%)	7637 (94.8%)	2.21
Police co-attendance (%)	244 (38.9%)	2542 (31.1%)	16.62***
Public outdoors places (%)	133 (21.7%)	1186 (14.8%)	20.80***
Metro areas (%)	519 (82.8%)	6278 (76.8%)	11.87***
Self harm-related (%)	107 (17.1%)	2363 (28.9%)	40.25***
Reported history of psychosis (%)	147 (23.4%)	3607 (44.1%)	101.35***

[a]Median length (mins) of attendance: time arrived at patient to time to clear the attendance.
*** $p < 0.05$.

men, presenting in metropolitan outdoor areas, and involved police co-attendance, compared with non-drug-related attendances. In addition, significantly more individuals with non-drug-related psychosis had a self-reported past history of psychosis, and had presentations that involved self-harm.

These findings demonstrate that a proportion of individuals who use stimulants may develop transient psychotic symptoms that require intervention by acute health services. While previous studies have identified that the presenting symptoms of stimulant-related psychosis may be indistinguishable from non-drug-related psychosis (Hermens et al., 2009), these data do demonstrate a number of socio-demographic factors that differ between the two types of acute presentations.

Acknowledgements

The authors would like to acknowledge and kindly thank Ambulance Victoria and its paramedics for their entry of data used in this study.

Declaration of interest

Dan Lubman has received speaking honorarium from AstraZeneca and Janssen, as well as provided consultancy advice to Lundbeck.

Funding

This project is a collaborative project between Turning Point and Ambulance Victoria and is funded by the Victorian Department of Health and Human Services and Commonwealth Department of Health and Aging.

Note

1. The *Ambo project*, a unique drug-related surveillance project that analyses and codes paramedic records for the purpose of monitoring drug-related trends and harms (Lloyd and McElwee, 2011). In 2012, the Ambo project expanded to include monitoring of drug-, self-harm- and mental health-related acute presentations.

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4.2 Discussion and summary

In this study, we identified that people presenting with acute psychotic symptoms and MA use were more likely to be younger, male and with no previous psychiatric history or self-harm involvement compared to acute presentations of non-drug related psychosis. Importantly, we also identified that acute presentations of MAP contributed to a similar burden on acute services as presentations of primary psychosis, in terms of time of attendance by paramedics, and proportion transported to hospital. This highlights the significant impact of MAP on the health system, supporting the need to explore risk factors that may be modifiable.

This study was conducted on a large dataset of specifically coded patient care records. Strengths include the size of this database, robust methodology, and representativeness in terms of acute presentations. However, it does not reflect non-acute presentations of MAP in the community; nor presentations of MAP in alcohol and other drug (AOD) treatment populations. The latter will be explored in the next study.

Chapter 5

Study 2: Clinical correlates of MAP in AOD treatment seekers

5.1 PREAMBLE

In Chapter 4, we investigated demographic correlates of MAP in an acute ambulance dataset. Here, we sought to explore correlates of MAP in a clinical alcohol and other drug (AOD) outpatient treatment population. The results of this study are presented in the following manuscript.

Declaration for Thesis Chapter 5

Monash University

Declaration by candidate

In the case of Chapter 5, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation, data collection, data analysis, manuscript preparation	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution
Margret Petrie	Data collection
Michelle Sharkey	Data collection
Prof Dan Lubman	Supervision and review of manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 02/09/18
Main Supervisor's Signature	[redacted]	**Date** 02/09/18

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Addiction

AUSTRALASIAN PSYCHIATRY

Australasian Psychiatry
2017, Vol 25(3) 246–249

DOI: 10.1177/1039856216684737
journals.sagepub.com/home/apy
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Key differences in treatment-seeking stimulant users attending a specialised treatment service: a means of early intervention?

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Abstract

Objectives: Few people who use stimulants seek clinical treatment. This study sought to describe a cohort of stimulant users who attended a stimulant-specific treatment service, *Access Point*, in Melbourne, Australia between 2008 and 2014.

Methods: A retrospective audit of the records of adults (n = 175) who sought treatment for stimulant use at a stimulant-specific outpatient treatment service was conducted.

Results: Service users had a median age of 32 (range = 19–54). Most stimulant users were in part- or full-time employment (53.6%) and had stable accommodation (85%). There was a high rate of mental health comorbidity, with over half (52%) reporting a previous history of mental health problems, while one-third (33%) reported previous suicide attempts. There was a high rate (48%) of previous methamphetamine-associated psychosis, which was significantly correlated with frequency of use (x^2 = 13.698, p = 0.008).

Conclusions: This study supports the potential of a targeted and specialised treatment service as a means of early intervention for stimulant users. The high prevalence of methamphetamine-associated psychosis history in this group suggests that frequent use of stimulants increases the risk of psychosis, even among high-functioning individuals.

Keywords: methamphetamine, stimulant, addiction, dual diagnosis, psychosis

The use of amphetamine-type stimulant drugs has become a rapidly growing problem worldwide over the past five years,[1] particularly in parts of South East Asia and, more recently, North America and Australia. In these regions, psychostimulant drug use, and particularly methamphetamine use, contributes to an increasing proportion of people receiving treatment for drug use disorders.[1]

However, research suggests there continues to be a large treatment gap for stimulant use disorders, and few individuals with problematic use seek clinical care.[2] Many alcohol and other drug (AOD) treatment services have traditionally been set up to treat opioid or alcohol use disorders, and individuals who use stimulants often present with different risks and needs. While clinicians in mainstream services are experienced in recognising and responding to common physical complications of opioid or alcohol use disorders, they may be less skilled in screening, assessing or treating psychological harms, which can be more common and often more severe in methamphetamine users in comparison to other drug users.[3]

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For instance, symptoms of psychosis are a common psychological harm associated with regular methamphetamine use. Indeed, the prevalence of methamphetamine-associated psychosis varies from 15%–23% in recreational or community settings to up to 60% in dependent users in treatment settings.[4–7] Although the evidence suggests that this is a common risk associated with methamphetamine use, such symptoms may be missed or mismanaged in mainstream services, and the nature and correlates of psychosis risk in treatment-seeking populations remain poorly understood.

A psychostimulant-specific specialist treatment clinic (*Access Point*) was established and promoted in Melbourne, Australia in 2008 to address the specific needs of this population. *Access Point* was the only stimulant-specific treatment service in the state of Victoria during its period of operation from 2008 to 2014. It aimed to deliver medically supported psychological counselling treatment to individuals seeking help for stimulant use disorders, and was staffed by experienced professionals, including a clinical psychologist, social worker, nurse, psychiatrist and addiction medicine specialist. Staff were specifically trained in the screening, assessment and treatment needs of stimulant users, and routinely assessed for mental health harms associated with methamphetamine use, such as methamphetamine-associated psychosis.

This study seeks to describe the demographic, social and substance use characteristics of treatment-seeking methamphetamine users presenting to *Access Point* during its years of operation, as well as directly comparing this sample to other Australian studies of methamphetamine-using adults. The study also seeks to determine the relationship between presenting characteristics and mental health harms experienced by methamphetamine users in this sample, particularly focusing on the correlates of methamphetamine-associated psychosis risk.

Methods

A retrospective clinical audit of the records of adults who sought treatment for stimulant use at the *Access Point* clinic was conducted. Over a period of six years (2008–2014), the clinic provided care to over 200 people. Only records including complete assessments were included in this audit (n = 175). Some 62 records were excluded due to non-attendance or incomplete assessments.

The clinical record contained information routinely gathered during a structured assessment process, including self-reported mental health history and experiences of psychotic symptoms associated with methamphetamine use. Demographic data, information regarding drug use and drug use history, and current and past mental health history was also collected. There was no exclusion of any individuals with self-reported previous mental health disorders. In terms of drug use, the following information was recorded for the primary stimulant drug used: type of stimulant drug, primary route of use (intravenous injecting, inhalation/smoking, snorting or other), average amount of drug used per occasion (in grams), frequency of use and estimated duration of use.

Three clinicians at the service audited the clinical records using a standardised data collection tool (SA, MS and MP). The auditing clinicians met regularly over the course of the study to verify the accuracy of data and to ensure consistency in data collection methods.

The socio-demographic and drug use characteristics of this sample were compared to three other populations from other studies conducted in Australia over this period – a sample of adults seeking residential detoxification treatment for methamphetamine use and a sample of adults seeking residential rehabilitation treatment for methamphetamine use (reported in the same study),[8] and a community-based sample of non-treatment seeking methamphetamine-using adults in Melbourne.[9]

Statistical analysis

Descriptive statistics were calculated to characterise the study sample. Univariate logistic regression analysis was utilised to investigate the associations between socio-demographic, health and substance use variables and methamphetamine-associated mental health harms, including psychosis. All data analysis was undertaken using SPSS version 22.0.

Results

Service users had a median age of 32 (range 19–54 years, interquartile range 26–39 years) and over three quarters (78%) were male. The majority were in part- or full-time employment (53.6%), and 10% of individuals were accessing a disability support pension. Most individuals (85%) reported being in stable accommodation (defined as their own home, private rental or a stable Ministry of Housing accommodation). In terms of sexual orientation, while the majority of individuals identified as heterosexual, 21.5% were homosexual (lesbian/ gay). Most people (60.5%) accessing this service had never sought AOD treatment before.

Nearly three-quarters (73.7%) were seeking treatment for crystalline methamphetamine use, and almost half of this group stated that their main route of use was inhalation or smoking (49.4%), with 39.5% reporting regular injecting use. Poly-drug use was very common, and almost all individuals (92.6%) reported at least weekly use of other substances, most commonly alcohol (56.6%) or tobacco (52.3%); cannabis use was present in 40.2% of individuals.

The median amount of stimulant used was 0.5 g per occasion (range 0.1–5.0 g), and most individuals reported using weekly or less than weekly (44%), with less than five years' duration of use (53%).

Table 1. Client socio-demographic and drug use characteristics compared with other samples in Australia

Variable	Access Point *clinic*	*Treatment sample (detoxification)*[8]	*Treatment sample (residential rehabilitation)*[8]	*Community non-treatment-seeking sample*[9]
n	175	112	248	255
Gender (male)	78%	72%	77%	64%
Age (median/mean years)	32	32	31	30
Unstable accommodation	15%	13%	5%	44%
Unemployed	44%	74%	89%	74%
No previous AOD treatment	61%	27%	12%	27%
Injecting drug use	39%	73%	67%	62%
Frequency of use more than weekly	56%	N/A	N/A	64%

AOD: alcohol and other drug.

Comparison to other samples

The socio-demographic and drug use characteristics of this sample were compared to two other Australian treatment-seeking populations[8] and a non-treatment-seeking sample[9] (see Table 1). Based on this comparison, clients attending *Access Point* were more likely to be employed and in stable accommodation compared to stimulant users in the other samples. In terms of drug use patterns, there were lower levels of injecting drug use among clients of *Access Point*. Direct comparisons were unable to be conducted for frequency, duration and average amount of use; however, overall, it appeared that the *Access Point* clinic saw individuals who reported lower levels and less frequent use for a shorter duration of time in comparison to the other treatment-seeking samples.[8]

Mental health

There was a high rate of mental health comorbidity in this group, with 36% currently being prescribed psychotropic medications, and 52% self-reporting a previous history of mental health problems. A third (33%) of individuals reported a history of previous suicide attempts.

Methamphetamine-associated psychosis

Nearly half of the cohort self-reported a previous history of psychotic symptoms associated with their use (48%). The likelihood of psychosis was significantly higher in those using more than weekly ($x^2 = 8.039$, $p = 0.005$), with a previous mental health history ($x^2 = 13.823$, $p = 0.000$), previous suicide attempts ($x^2 = 13.943$, $p = 0.000$), or prescribed current psychotropic medication ($x^2 = 16.932$, $p = 0.000$) (See Table 2). There was no significant correlation between the likelihood of psychosis and duration of use ($x^2 = 0.069$, $p = 0.793$) or route of use (injecting versus non-injecting use; $x^2 = 1.904$, $p = 0.168$).

Discussion

This study is the first to examine a cohort of treatment-seeking stimulant users in Melbourne. A key finding of this study was the socio-demographic characteristics of this cohort, which differed from previous samples of non-treatment-seeking regular methamphetamine users in Melbourne,[9] as well as treatment-seeking samples of methamphetamine users in other parts of Australia.[8] The clinic was attended by a substantially higher proportion of individuals in stable accommodation who were more likely to be employed, while 61% reported that they had not accessed AOD treatment in the past. Clients of *Access Point* also reported a shorter duration of stimulant use, and a lower proportion of injecting drug use compared to other Australian samples.[8,9] Some of these differences may relate to the focus on clients recruited from residential detoxification or rehabilitation settings[8] rather than outpatient counselling services as in the current study.

Previous research has highlighted a large treatment gap for methamphetamine use disorders, with only about a third of individuals with problematic use accessing treatment.[2] The data from this audit suggests that this stimulant-specific service attracted a subset of higher functioning regular stimulant users who would not otherwise have accessed care, and who were presenting earlier in the natural history of their substance use trajectories compared to other treatment services. This supports the need for targeted stimulant-specific counselling services, with separate entry pathways to mainstream services, as a solution for early intervention for stimulant users.

The prevalence of mental health problems and methamphetamine-associated psychosis in this group was high, and was comparable to that observed in other cohorts with higher levels of methamphetamine use and relative socioeconomic disadvantage.[6,10] Furthermore, the

Table 2. Substance use and mental health history by methamphetamine-associated psychosis

Variable	*Total (%)*	*Methamphetamine-associated psychosis (N = 164)*		*Pearson chi-square statistic*	P-*value*
		Yes (N = 79) N (%)	*No (N = 85) N (%)*		
Frequency of use					
Weekly or less	70 (43)	25 (32)	45 (54)	**8.039**	**0.005**
More than weekly (>8/28)	91 (57)	53 (68)	38 (46)		
Duration of use					
< 5 years	87 (53)	43 (54)	44 (52)	0.069	0.793
5 years or more	76 (47)	36 (46)	40 (48)		
Main route of administration					
Injecting	65 (40)	36 (46)	29 (35)	1.904	0.168
Previous mental health history					
Yes	91 (53)	54 (68)	33 (39)	**13.823**	**0.000**
Previous history of suicide attempts					
Yes	56 (33)	37 (48)	17 (20)	**13.943**	**0.000**
Current psychotropic medications					
Yes	63 (36)	41 (53)	18 (21)	**16.932**	**0.000**

predictors of methamphetamine-associated psychosis in this study concurred with risk factors identified in other studies, such as increasing frequency of use[5,10] and a past history of mental health problems.[11] However, methamphetamine-associated psychosis is a complex phenomenon, and this clinical audit is limited in its ability to establish whether self-reported symptoms of psychosis were pre-existing, or arose during periods of drug use or withdrawal.

In terms of other limitations, the data presented here were collected as part of routine clinical care, and there are gaps arising from missing data and the lack of standardised measures of outcomes. While limitations also exist in relation to participant self-report, previous studies have demonstrated that self-report does serve as a valid and reliable means of documenting drug use and related problems.[12]

Conclusions

This study supports the potential of a targeted and specialised treatment service as a means of early intervention for stimulant users. The high prevalence of methamphetamine-associated psychosis in this group is consistent with previous studies, and highlights the substantial burden of mental health problems experienced by individuals who use stimulants regularly.

Disclosure

The authors report no conflict of interest. No funding was received for this study. The authors alone are responsible for the content and writing of the paper

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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5.2 Discussion and Summary

This study demonstrated the frequency of methamphetamine use was significantly correlated with the likelihood of a lifetime experience of psychotic symptoms in this sample of treatment-seeking methamphetamine users. This is consistent with the previous literature, even though the sample of treatment-seekers in this study could be considered higher functioning in comparison to previous Australian samples. This study therefore provides further support for methamphetamine use as a strong modifiable risk factor for MAP.

Chapter 6

Study 3: A systematic review of risk factors and correlates of MAP

6.1 PREAMBLE

As highlighted in the introduction (Chapter 1) and the literature review (Chapter 2), studies on methamphetamine-associated psychosis have been conducted in a variety of populations with differing definition and measurement of the outcome of psychosis. Consequently, it is difficult to get an understanding of the key risk factors and predictors for the disorder. In the following paper, we sought to consolidate the contemporary literature on predictors and correlates of MAP using systematic review methodology.

Declaration for Thesis Chapter 6

Monash University

Declaration by candidate

In the case of Chapter 6, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation, review protocol, search and data extraction, manuscript preparation	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution
Dr James Foulds	Systematic search, data extraction
A/Prof Rebecca McKetin	Review of manuscript
Prof Dan Lubman	Supervision and review of manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 02/09/18
Main Supervisor's Signature	[redacted]	**Date** 02/09/18

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Review

ANZJP

Australian & New Zealand Journal of Psychiatry
1–16
DOI: 10.1177/0004867417748750

A systematic review of risk factors for methamphetamine-associated psychosis

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Abstract

Objective: Chronic methamphetamine use is commonly associated with the development of psychotic symptoms. The predictors and correlates of methamphetamine-associated psychosis are poorly understood. We sought to systematically review factors associated with psychotic symptoms in adults using illicit amphetamine or methamphetamine.

Methods: A systematic literature search was performed on MEDLINE (OVID), PsycINFO and EMBASE databases from inception to 8 December 2016. The search strategy combined three concept areas: methamphetamine or amphetamine, psychosis and risk factors. Included studies needed to compare adults using illicit methamphetamine or amphetamine, using a validated measure of psychosis, on a range of risk factors. Of 402 identified articles, we removed 45 duplicates, 320 articles based on abstract/title and 17 ineligible full-text articles, leaving 20 included studies that were conducted in 13 populations. Two co-authors independently extracted the following data from each study: country, setting and design; participant demographic and clinical details; sample size; measure/s used and measures of association between psychosis outcomes and risk factors. Individual study quality was assessed using a modified Newcastle-Ottawa Scale, and strength of evidence was assessed using GRADE criteria.

Results: Frequency of methamphetamine use and severity of methamphetamine dependence were consistently found to be associated with psychosis, and sociodemographic factors were not. There was inconsistent evidence available for all other risk factors. Individual study quality was low–moderate for the majority of studies. Heterogeneity in study outcomes precluded quantitative synthesis of outcomes across studies.

Conclusion: The most consistent correlates of psychotic symptoms were increased frequency of methamphetamine use and dependence on methamphetamine. The findings of this review highlight the need for targeted assessment and treatment of methamphetamine use in individuals presenting with psychosis.

Keywords

Methamphetamine, psychosis, substance-induced psychosis, risk factor, dual diagnosis

Introduction

Amphetamine and methamphetamine (hereafter referred to as MA) are potent and addictive synthetic stimulant drugs that are widely used internationally. Illicit MA use is a growing public health concern globally, in part due to psychological harms such as psychosis (McKetin et al., 2017). Experimental studies have shown that psychosis symptoms triggered by MA correlate with excessive striatal dopamine release (Cruickshank and Dyer, 2009), with some studies supporting a phenomenon of sensitisation arising from increasing vulnerability of dopamine

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receptors to continuing MA use (Bramness and Rognli, 2016; Curran et al., 2004). Acutely, symptoms of psychosis can be extremely distressing for the individual and affected others and contribute to significant burden on health services (Arunogiri et al., 2015; McKetin et al., 2017).

The term methamphetamine-associated psychosis (or MAP) has been proposed to refer to the spectrum of psychotic symptoms that can occur in MA users (Mathias et al., 2008). This can range from transient intoxication states to longer-lasting substance-induced psychotic disorders or more persistent syndromes that resemble schizophrenia (Bramness and Rognli, 2016). Japanese authors have also described a phenomenon known as 'flashbacks' where abstinent ex-MA users experience a recurrence of psychoses in the absence of the drug (Yui et al., 2002). Studies have suggested that the prevalence of MAP in cohorts of illicit MA users varies between 15% and 23% in recreational or community settings to up to 60% in dependent users in treatment settings (Arunogiri et al., 2017; Chen et al., 2003; Ding et al., 2014; Hides et al., 2015; Lapworth et al., 2009; McKetin et al., 2010, 2013). Variability in the prevalence of psychosis symptoms may relate to MA doses and patterns of use, but this does not appear to fully account for the phenomenon – there are subsets of individuals who do not appear to develop psychotic symptoms with frequent MA use, and conversely, some who experience chronic psychosis following limited exposure to the drug (Akiyama et al., 2011; Salo et al., 2013). Taken together, these findings suggest the need to look for potential correlates of psychosis beyond MA use.

The concurrent use of alcohol or other drugs, co-morbid psychiatric disorders and family history have all been examined for associations with psychosis risk (Bramness and Rognli, 2016). However, there remains uncertainty related to these associations due to individual study limitations – such as small or poorly representative samples or inadequate control for confounding factors. Many studies have compared individuals using MA who develop psychosis against healthy controls rather than other MA users. There is great variability in the measurement of psychosis, with some studies reporting diagnoses of psychotic disorders and others measuring symptoms of psychosis. In addition, some studies have not sufficiently accounted for or excluded individuals with primary psychotic disorders. Although there have been three previous narrative reviews focussing on factors associated with MA psychosis (Bramness et al., 2012; Glasner-Edwards and Mooney, 2014; Rognli and Bramness, 2015), these have not utilised systematic methodology and have not attempted to evaluate the quality of studies or potential sources of bias.

As such, we aimed to conduct a systematic review of the existing literature in order to provide higher quality evidence on correlates of MAP. Developing a greater understanding of the factors associated with psychosis in individuals using MA assists in building a profile of high-risk individuals, allowing better targeting of clinical approaches within acute mental health and addiction settings.

Method

A systematic review of studies measuring psychosis symptoms in adults using illicit MA was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Details of the systematic review protocol were registered on PROSPERO International Prospective Register of Systematic Reviews (Registration: 42016052223) prior to data extraction.

Studies were included if they met the following criteria: (1) participants were adult (>17 years) humans with current use (within the last 12 months) of illicit MA or amphetamine (MA); (2) participants using MA with current or lifetime psychosis symptoms (referred to as MAP) were compared with those using MA without psychosis symptoms (MNP), where psychosis was measured using a validated instrument or structured interview and (3) individuals identifying MA as their primary drug were identified and analysed separately from those citing other substances as their primary drug.

Electronic searches were performed on the following databases: MEDLINE (OVID), PsycINFO and EMBASE databases, from the earliest available dates to 8 December 2016. The search strategy combined three concepts: MA or amphetamine, psychosis and risk factors. Search terms for MA included METHAMPHETAMINE, AMPHETAMINE, METHYL-AMPHETAMINE, METHAMPHETAMINE and METHAMFETAMINE; search terms for psychosis included DRUG-INDUCED PSYCHOSIS, SUBSTANCE-INDUCED PSYCHOSIS, PSYCHOSIS, PSYCHOSES, SCHIZOPHRENIA and SCHIZO-AFFECTIVE and search terms for risk factors included RISK FACTORS, VULNERABILITY FACTORS and PREDISPOSING FACTORS (see Appendix 1 for Medline search strategy). In databases where Medical Subject Headings (MeSH) terms were available, they were exploded and combined. No language restrictions were applied to the search.

The reference lists of previous reviews (Bramness et al., 2012; Bramness and Rognli, 2016) and articles identified in the main search were also screened for citations not identified in the main search. As this supplementary search identified five further citations, we elected to perform an additional search using Google Scholar to identify articles that had cited those articles identified in the main search in an effort to avoid missing any potentially relevant articles. The review protocol was updated to reflect this further search. Screening of titles, abstracts and subsequently full texts was performed independently by two authors (S.A. and J.A.F.). Any disagreements regarding study inclusion were resolved by discussion.

Study design and data extraction

Single-case reports, literature reviews and studies in animals were excluded. The following data were extracted from studies: study country, setting and design; participant demographic and clinical details; sample size; measure/s used and measures of association between risk factors and psychosis outcomes. Studies were categorised based on whether psychosis was assessed using a current or lifetime measure. Risk factors were classified according to the following categories: (1) sociodemographic factors (including age, gender, employment, educational status, housing status and socioeconomic status); (2) MA use patterns (including measures of MA use, amount, frequency, duration of use, age of onset of use and route of use); (3) other drug use; (4) psychiatric comorbidity (including current and previous psychiatric illness and personality disorders); (5) family history (of psychotic or other psychiatric illness) and (6) history of trauma.

An electronic data extraction tool was piloted on one study, refined and subsequently used by two authors (S.A. and J.A.F.) to independently extract data from each included study. Multiple studies conducted on the same population were combined, and data were then extracted together as one study. Where there were uncertainties about the data in studies, or where MA-specific outcomes were not reported, we contacted authors for further clarification and re-analysis of original data.

Quality assessment

As there is no accepted gold standard instrument for assessing quality of observational studies, a modified version of the Newcastle–Ottawa Scale (Wells et al., 2011) was developed specifically for use in this review. The studies were scored on the following domains: (1) representativeness of the cohort (out of 3), (2) assessment of risk factor (out of 3), (3) demonstration that psychosis was not present at the start of the study (out of 2), (4) comparability of the two groups and controls for confounding (out of 2) and (5) assessment of the outcome of psychosis (out of 3), with a final quality score out of 13. S.A. and J.A.F. independently assessed the quality of included studies, with final scores derived by consensus between those two authors. Based on evidence across studies, outcome-level quality for each predictor was assessed by consensus between two authors with reference to the GRADE criteria, considering study design, study quality, consistency and directness for each predictor (Atkins et al., 2004). Inconsistency in evidence was determined by consideration of qualitative study heterogeneity, variation in effect sizes, study populations and outcome definition with reference to the Cochrane guidelines (Schunemann and Santesso, 2011).

Study synthesis

Meta-analysis was planned for correlates reported consistently across three or more studies, where heterogeneity was acceptable. However, lack of consistency in reporting prevented meta-analysis for any correlates, therefore synthesis of results was by narrative review.

Results

Study characteristics

A total of 20 papers met the inclusion criteria, which were based on studies in 13 different sample populations and a total of 5476 individuals (Figure 1). The main reasons for excluding studies were ineligible study design (e.g. case report or literature review), a lack of comparison between MAP and MNP groups and a mixed substance-using population where there was no data available specific to primary MA users.

The characteristics of the 13 studies are summarised in Table 1. Four studies were conducted in Asia (China, Taiwan, Thailand and Malaysia), five in Australia, three in the United States and one in Sweden. There was a great deal of variability in the method used to define and assess psychosis. Less than half the studies assessed current symptoms of psychosis (Studies 1–4) or a psychotic disorder (Study 5), compared to a lifetime disorder (Studies 6–10) or symptoms (Studies 11–13).

Risk of bias within studies

Individual study quality varied considerably with the total quality ratings ranging from 5 to 12 (mean quality score = 7.85, standard deviation [SD] = 2.08; see Table 3 – Online Appendix). The most common reasons for lower quality were the lack of exclusion of a pre-existing psychotic disorder among participants and insufficient control for confounding factors such as other drug use (Figure 2).

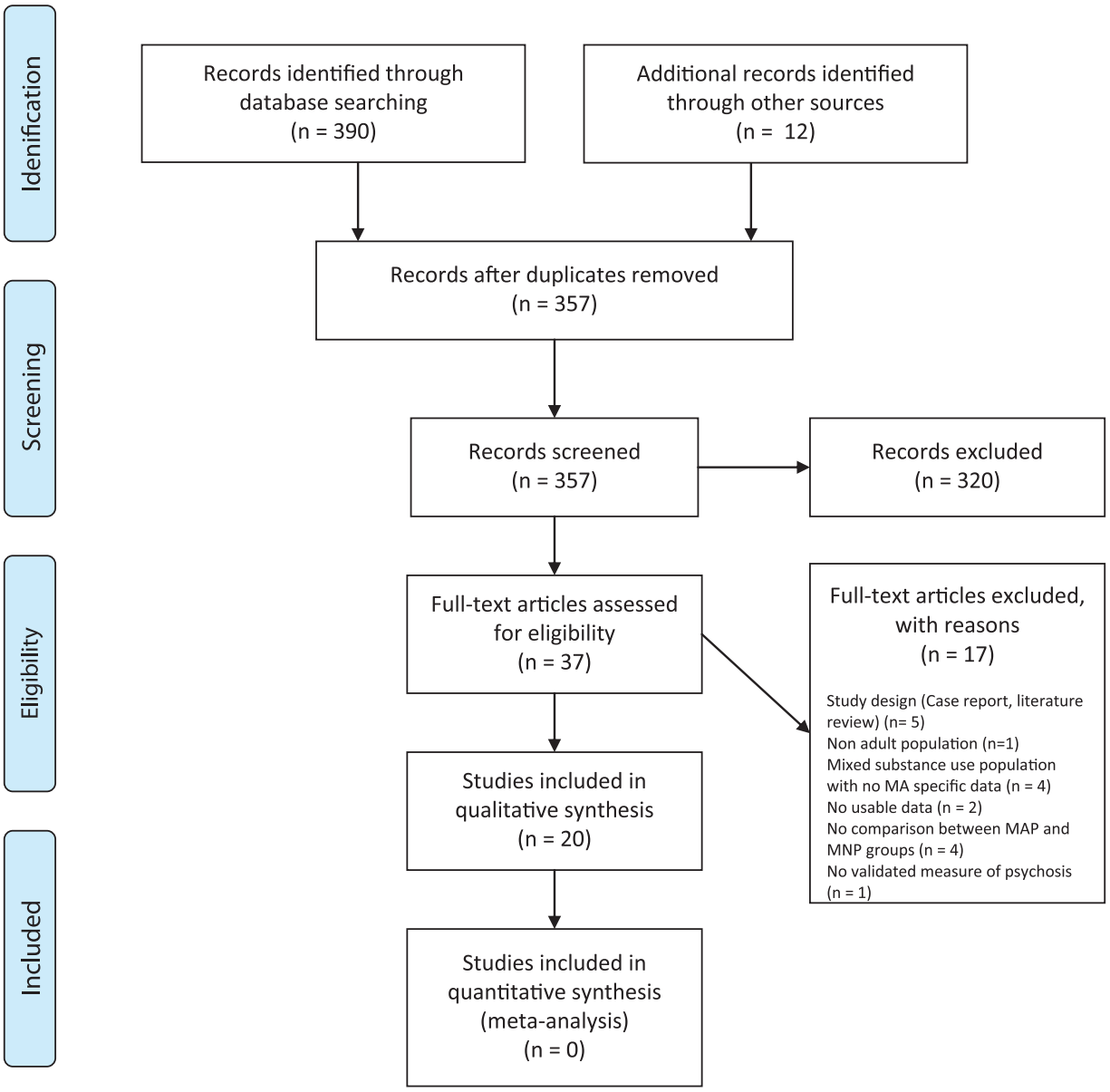
Results of individual studies-correlates of MAP

Results of individual studies are presented in Table 2. The included studies compared individuals using MA with and without psychosis on the following factors.

Sociodemographic factors. Age, gender or employment status were not associated with MAP in any study. One study found that fewer years of schooling (OR = 0.8, 95% confidence interval [CI] = [0.7, 1.0]) and homelessness in the past month (OR = 2.5, 95% CI = [1.1, 5.3]) were significant predictors of hospitalisation for substance-induced psychosis (Rognli et al., 2014). Six other studies did not find any association between years of education and psychosis risk (Chen et al., 2003; 2005, 2007; Ding et al., 2014; Hides et al., 2015; Lin et al., 2004; McKetin et al., 2006; Salo et al., 2013; Sulaiman et al., 2014).

Patterns of MA use. Nine studies found associations between MA-related factors (dose – amount or frequency; duration

Figure 1. PRISMA flow diagram.



– age of onset or years of use; severity of dependence or route of use) and MAP risk, and the remaining four (Glasner-Edwards et al., 2008; McKetin et al., 2010; Rognli et al., 2014; Salo et al., 2013) reported no association (Table 2).

Three of the studies that did not find an association reported psychosis outcomes based on lifetime symptoms (Salo et al., 2013), substance-induced disorders (Glasner-Edwards and Mooney, 2014) or hospitalisation (Rognli et al., 2014). The fourth study was conducted in a sample with very low frequency of MA use, with only 12% of participants reporting weekly or more frequent use (McKetin et al., 2010). In general, the studies that did not find an association were of lower quality and were vulnerable to selection and recall bias (Tables 1 and 2).

Duration – age of onset or number of years of MA use. There was inconsistent evidence for both age of onset of MA use and number of years of use. The majority of the studies that found an association between these factors and psychosis used lifetime measures of psychotic disorder (Chen et al., 2003; Ding et al., 2014) or symptoms (Kalayasiri et al., 2009). These studies were also mainly conducted in Eastern Asian populations(Chen et al., 2003; Ding et al., 2014; Kalayasiri et al., 2009), suggesting there may be

Table 1. Characteristics of included studies.

Study		Design	Sample	Measure of psychosis[a]	Correlates of psychosis	Quality[b]	Comments
Current measures of psychosis symptoms							
1	McKetin et al. (2006) (Australia)	Cross-sectional	*N* = 309 Mixed community sample 66% injecting main route 5% Previous diagnosis of schizophrenia and further 5% previous other psychotic disorder	BPRS Current (past month)	• Frequency of MA use and MD • not associated with age, sex, employment status, education, birth place, injecting use, age of first use or affective or anxiety disorder	++	Convenience sample which included a subset of individuals with a primary psychotic illness
2	Dawe et al. (2013) Lapworth et al. (2009) (Australia)	Cross-sectional	*N* = 329 49% methamphetamine dependent Inner city needle exchange programme 100% injecting main route Did not exclude individuals with a history of psychotic disorder	BPRS Current (past month)	• Severity of MD	+	Potential selection bias as all injecting drug use cohort. Did not control for other drug use as a confounding factor
3	McKetin et al. (2010) (Australia)	Cross-sectional	*N* = 75 Dance venue patrons 1.3% injecting main route; weekly use of other drugs in <10%. Individuals with a history of psychotic disorder excluded from analysis	Psychosis Screen Current (past year)	• Polydrug use • not associated with any sociodemographic factors (age, gender, employment) or MA use variables (age of onset, frequency, injecting route)	+	Potential selection bias and very low frequency of MA use in this sample
4	McKetin et al. (2013, 2006) (Australia)	Cohort	*N* = 278 Methamphetamine-dependent outpatient drug treatment; 79% injecting main route 3-year follow-up Individuals with a lifetime history of schizophrenia/manic episode excluded	BPRS Current (past month)	• current frequency of MA use; concurrent frequency of cannabis use and alcohol use • not associated with current substance use other than cannabis and alcohol • transient symptoms associated with male, earlier onset MA use, history of conduct and anxiety disorders; persistent symptoms associated with conduct disorder, anxiety disorder, depression and family history of psychotic disorder	+++	Sample mainly comprised individuals with severe MA dependence. Many confounding factors accounted for by within-subject comparison. Transient and persistent psychosis symptoms defined by past month symptoms at three separate timepoints (3 months, 1 year and 3 years)

(Continued)

Table 1. (Continued)

Study		Design	Sample	Measure of psychosis[a]	Correlates of psychosis	Quality[b]	Comments
Current measures of psychotic disorder							
5	Hides et al. (2015) (Australia)	Cross-sectional	*N* = 198 Needle syringe programmes 84% past month injecting use 12-month prospective study Did not exclude individuals with a history of psychotic disorder	PRISM-IV Lifetime and current psychotic disorder (substance induced or primary)	• Earlier age of onset of MA use • Family history of schizophrenia and bipolar disorder • Not associated with any sociodemographic variables or MA frequency or severity of dependence	++	Potential selection bias as sample recruited from needle syringe programmes. Both current and lifetime measures of psychotic disorder; Lifetime psychotic disorder was correlated against static risk factors (sociodemographic factors, family history) and current psychotic disorder against current factors (methamphetamine frequency, severity of dependence)
Study		Design	Sample	Psychosis outcome measure[a]	Correlates of psychosis	Quality[b]	Comments
Lifetime measures of substance-induced psychotic disorder							
6	Chen et al. (2003, 2005, 2007); Lin et al. (2004) (Taiwan)	Cross-sectional	*N* = 445 Lifetime MA use psychiatric hospital and detention centre History of psychosis prior to MA use or history of MA use <20 times per year excluded	DIGS-C MA-induced psychotic disorder	• Younger age at first MA use and larger quantities of MA used but not a longer duration of MA use • primary and substance-induced depression; suicide attempts; alcohol dependence; ASPD • higher familial morbid risk of schizophrenia, depression and bipolar disorder • not associated with gender, age, education or presence of non-substance-related criminal conviction	++	Recruitment from hospital and detention centre may be non-representative. Lifetime measure of psychosis subject to recall bias. Did not measure or control for other drug use as a confounding factor
7	Zweben et al. (2004); Glasner-Edwards et al. (2008) (USA)	Cross-sectional	*N* = 526 Methamphetamine-dependent outpatient drug treatment 3-year follow-up Did not exclude individuals with history of psychotic disorder	MINI MA-induced psychotic disorder	• Higher odds of hospitalisation and lifetime suicide attempt • not associated with frequency of MA use or use within past 30 days	++	Subset of participants from a larger study. Did not control for other drug use as a confounding factor

(Continued)

Table 1. (Continued)

Study		Design	Sample	Psychosis outcome measure[a]	Correlates of psychosis	Quality[b]	Comments
8	Sulaiman et al. (2014) (Malaysia)	Cross-sectional	*N* = 292 Methamphetamine dependent inpatient psychiatry unit and drug rehabilitation centre Excluded history of schizophrenia or primary psychosis.	MINI MA-induced psychotic disorder	• major depressive disorder • not associated with age, income, ethnicity, education level, employment, marital status, bipolar disorder, anxiety disorder, other substance use disorders, ASPD, duration of MA use, money spent on MA use or route of MA use	++	Lifetime measure of psychosis may be subject to recall bias.
9	Ding et al. (2014) (China)	Cross-sectional	*N* = 189 Residential rehabilitation Did not exclude individuals with a history of psychotic disorder.	MINI-plus MA-induced psychotic disorder	• duration of use, frequency of use, history of other drug use and childhood abuse exposure • not associated with MA dependence	++	Low frequency of MA use in this sample. Lifetime measure of psychosis may be subject to recall bias.
10	Rognli et al. (2014) (Sweden)	Cohort (retro-spective)	*N* = 1709 68.5% injecting main route prison sample 4- to 9-year follow-up Individuals with pre-existing psychotic disorder unlikely to be included, but not systematically screened for	Hospitalisation during 4- to 9-year follow-up Both primary and substance-induced psychosis reported; data extracted for substance-induced psychosis outcome	• Years of education and homelessness in past month • not associated with gender, age, years of employment, age of onset of MA use, duration of MA use, MA use frequency in month prior to incarceration, route of MA administration, family history of psychiatric problems, sexual abuse or physical abuse	+	Potential selection bias, as cohort recruited from prison. MA use measured at baseline; hospitalisation for substance-induced psychosis measured during 4- to 9-year follow-up period based on hospital coding. Did not control for other drug use.
Lifetime measures of psychosis symptoms							
11	Kalayasiri et al. (2009, 2014) (Thailand)	Cross-sectional	*N* = 727 Methamphetamine-dependent drug treatment programme 98.3% smoking route Did not exclude individuals with a history of psychotic disorder	MEQ MA-induced paranoia	• Younger age at first MA use; quantity and frequency of MA use during heaviest use period; lifetime number of episodes of MA use; MD severity; ASPD; history of suicide attempts; social phobia; pathological gambling; nicotine dependence and alcohol dependence • MAP was not associated with age, gender, ethnicity, marital status, employment or income	+	Lifetime measure of psychosis may be subject to recall bias and only assessed paranoia. Did not control for other drug use as a confounding factor

(Continued)

Table 1. (Continued)

Study		Design	Sample	Psychosis outcome measure[a]	Correlates of psychosis	Quality[b]	Comments
12	Smith et al. (2009) (USA)	Cross-sectional	*N* = 205 Amphetamine community outreach Did not exclude individuals with a history of psychotic disorder.	Questions based on CIDI	• Increasing MA use disorder severity	+	Mixed substance use sample. Data available specific to amphetamine use subset. Did not control for other drug use as a confounding factor
13	Salo et al. (2013) (USA)	Cross-sectional	*N* = 190 Methamphetamine-dependent drug treatment (*n* = 91) and residential housing (*n* = 99) No other current substance dependence Excluded participants with a history of psychotic disorder	MEQ MA-induced paranoia	• Not associated with any sociodemographic factors (age, gender and education); methamphetamine use factors (age of first use, duration of use, mean daily MA dose and months of abstinence); lifetime substance use disorders or family history of psychiatric illness	++	Lifetime measure of psychosis may be subject to recall bias and only assessed paranoia. Potential selection bias excluded anyone with co-morbid Axis I disorders (current or lifetime) or dependence on any substance other than MA or nicotine in past 5 years and participants had to be abstinent for at least 3 weeks

MA: methamphetamine; MD: methamphetamine dependence.

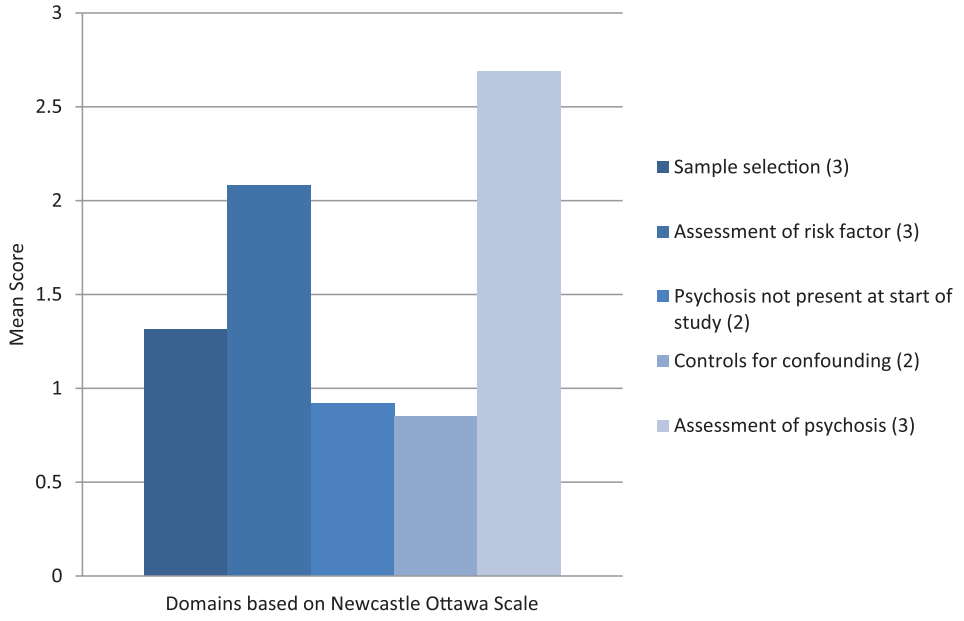
[a]Measures of lifetime psychotic disorder of methamphetamine-associated psychosis: PRISM-IV (Psychiatric Research Interview for Substance and Mental Disorders), MINI (Mini-International Neuropsychiatric Interview) and DIGS-C (Diagnostic Interview for Genetic Studies (Chinese)).

Measures of psychosis symptoms: BPRS (Brief Psychiatric Rating Scale), operationalised questionnaire based on CIDI (Composite International Diagnostic Interview), MEQ (Methamphetamine Experience Questionnaire) for paranoia when using MA and Psychosis Screen (validated 7-item screen assessing past year psychosis symptoms).

[b]Quality based on modified Newcastle–Ottawa Scale rating (see Table 3).

+: total score 0–6; ++: total score 6–10; +++: total score 11–13.

Figure 2. Risk of bias within studies.



cross-national variation in the association between duration of MA use and risk of psychosis.

Dose-amount and frequency of MA use. More frequent MA use was associated with a higher risk of psychosis in four studies (Ding et al., 2014; Kalayasiri et al., 2009; McKetin et al., 2006, 2013), the majority of which reported an outcome of current or lifetime psychosis symptoms. Conversely, four of the studies did not find this association (Glasner-Edwards et al., 2008; Hides et al., 2015; McKetin et al., 2010; Rognli et al., 2014) and three reported outcomes of lifetime substance–induced psychotic disorder. In general, the studies that found an association between MA frequency and MAP were of higher quality (Table 3 – Online Appendix) (Chen et al., 2003; 2005, 2007; Ding et al., 2014; Kalayasiri et al., 2009, 2014; Lin et al., 2004; McKetin et al., 2006, 2013, 2016; Sulaiman et al., 2014). Based on the results of these four studies, individuals using MA more frequently were estimated to have between 3 and 11 times greater odds of MAP compared to individuals with less frequent use (Ding et al., 2014; Kalayasiri et al., 2009; McKetin et al., 2006, 2013). One longitudinal study comprehensively controlled for a range of confounding factors including other drug use and demonstrated a within-subject dose-related relationship between MA dose (days of use) and concurrent risk of psychotic symptoms (McKetin et al., 2013). In this study, individuals using 16 or more days per month had significantly elevated odds of MAP compared to those using less than 16 days (OR = 11.2, 95% CI = [5.9, 21.1]) (McKetin et al., 2013). In terms of amount of MA use, three of the four studies that examined this predictor found that greater amounts of MA use correlated with a greater likelihood of a lifetime substance-induced psychotic disorder (Chen et al., 2003; Sulaiman et al., 2014) or symptoms (Kalayasiri et al., 2009).

Severity of MA dependence. There was also an association between increasing severity of MA dependence (as defined by *Diagnostic and Statistical Manual of Mental Disorders* [4th ed.; DSM-IV] symptom count or by a validated tool such as the severity of dependence scale [SDS] and MAP symptoms across four studies [Ding et al., 2014; Kalayasiri et al., 2009; Lapworth et al., 2009; Smith et al., 2009]). In comparison to non-dependent individuals, MA-dependent individuals were estimated to have between 2 and 3 times greater odds of developing MAP (Ding et al., 2014; Kalayasiri et al., 2009, 2014). One study did not find this association, but this was conducted in a sample recruited from needle syringe programmes with high injecting drug use, which may not have been comparable to other populations (Hides et al., 2015).

Route of MA use. Only four included studies examined the relationship between route of administration and MAP (McKetin et al., 2006, 2010; Rognli et al., 2014; Sulaiman et al., 2014). All of these studies did not find any association between injecting route of use and MAP. One study had a very low rate of injecting use in a recreational drug use sample (McKetin et al., 2010). Two of the studies reported outcomes of current psychotic symptoms (McKetin et al., 2006, 2010), one reported lifetime substance-induced psychotic disorder (Sulaiman et al., 2014) and one

Table 2. Summary of findings.

Risk factors	Total number of participants (studies)	Outcome(s)[a]	Comments (based on GRADE criteria)[b]
Sociodemographic variables			
Gender	3657 (6)	No association[1,3,5,6,10,11,13]	Consistent results across studies supporting no association between psychosis symptoms and most sociodemographic variables. Variety of studies in different settings and samples. One longitudinal study (Rognli et al., 2014) found an association between lower education and homelessness with a higher risk of MAP. This study had a higher threshold for psychosis, defining this as hospitalisation for a substance-induced psychotic episode
Age	3949 (8)	No association[1,3,5,6,8,10,11,13]	
Education (years of schooling)	1623 (6)	No association[1,5,6,8,9,13]	
	1709 (1)	More years of schooling associated with lower risk of hospitalisation for psychosis[10]	
Homelessness	198 (1)	No association[5]	
	1709 (1)	Past month homelessness associated with higher risk of hospitalisation for psychosis[10]	
Income	1019 (2)	No association[8,11]	
Employment	3314 (6)	No association[1,3,5,8,10,11]	
Methamphetamine use variables			
Age at onset	2287 (4)	No association[1,3,10,13]	Inconsistent results across studies. Two of the studies to find an association measured lifetime experiences of psychosis may be subject to recall bias; one study found an association based on lifetime substance-induced psychosis versus no psychosis
	1370 (3)	MAP significantly lower age of onset[5,6,11]	
Years of use	2636 (4)	No association[6,8,10,13]	Inconsistent results across studies. Only study that found an association measured lifetime psychosis and may have been subject to recall bias. Number of years of use does not account for changes in pattern of use or periods of abstinence
	189 (1)	Duration of use >4 years significantly associated with MAP[9]	
Amount of use	190 (1)	No association[13]	Consistent results across studies that measured current MA use amount. Only study that did not find association recruited abstinent participants who reported retrospective MA amounts. Current amount of MA use correlated with lifetime measure of psychosis in all studies leading to indirect measurement of outcome
	1464 (3)	MAP associated with greater amounts of use[6,8,11]	
Frequency of use	2503 (4)	No association[3,5,7,10]	Consistent results across higher quality studies that measured current MA use against current psychosis symptoms. Studies that did not find an association measured lifetime psychosis and were subject to recall bias. Given moderate–large effect sizes and a dose–response relationship identified by one study, the level of quality of evidence for this risk factor can be considered moderate.[b]
	1503 (4)	Increasing frequency of MA use associated with higher risk of psychosis symptoms[1,4,9,11]	

(Continued)

Table 2. (Continued)

Risk factors	Total number of participants (studies)	Outcome(s)[a]	Comments (based on GRADE criteria)[b]
Route of use (injecting)	2389 (4)	No association[1,3,8,10]	Consistent results across studies
Dependence	198 (1)	No association of severity of dependence against lifetime psychosis symptoms[5]	Consistent results across four studies. Study that did not find an association was conducted in a sample with high injecting drug use, recruited from needle syringe programmes, assessing lifetime psychosis symptoms.
	1577 (4)	Dependence associated with higher risk of psychosis symptoms[2,9,11,12]	
Other substance use			
Alcohol	292 (1)	No association[8]	Consistent results across higher quality and longitudinal studies
	1450 (3)	Alcohol dependence associated with higher risk of psychosis symptoms[4,6,11]	
Cannabis	278 (1)	Higher frequency of cannabis use associated with higher risk of psychosis[4]	Only assessed in one study
Polydrug use	482 (2)	No association[8,13]	Two studies found no association but based on retrospective recall of previous drug use and conducted in non-representative samples
	268 (2)	History of any other drug use associated with higher risk of MAP[8,12]	
Psychiatric co-morbidity			
Major depressive disorder	309 (1)	No association (lifetime affective disorder)[1]	Few studies assessed this. Difficult to distinguish substance-induced versus primary diagnoses of affective and anxiety disorders in the context of current methamphetamine and other drug use
	1015 (3)	Current major depressive disorder associated with lifetime psychosis[6,8] or persistent psychosis[4]	
Anxiety disorder	601 (2)	No association[1,8]	
	278 (1)	Current anxiety disorder associated with transient and persistent psychosis symptoms[4]	
Personality			
Schizoid/ schizotypal personality disorders	445 (1)	Two studies found an association between schizoid/schizotypal personality traits and increased odds of psychosis symptoms[6]	Only one study assessed this
Antisocial personality, conduct disorders	1742 (4)	Association with MAP[4,6,8,11]	Consistent association across four studies. Difficult to account for confounding factors that may relate to conduct or antisocial personality disorder diagnosis
Family history			
Family history of psychiatric disorder	2097 (3)	No association[5,10,13]	Inconsistent results across studies. Heterogeneity in definition and measurement of family history across studies
	912 (2)	Association between persistent psychotic symptoms and family history of psychotic disorder.[4] Higher risk of psychosis symptoms in individuals with family history of schizophrenia[6]	

(Continued)

Table 2. (Continued)

Risk factors	Total number of participants (studies)	Outcome(s)[a]	Comments (based on GRADE criteria)[b]
Trauma			
Sexual or physical abuse	1709 (1)	No association between lifetime sexual abuse or physical abuse and hospitalisation for psychosis[10]	Only one study to assess this
Childhood trauma	189 (1)	More adverse childhood events (ACEs) associated with higher risk of MAP. Significant positive association between lifetime psychosis and number of ACEs[9]	Only one study to assess this

[a]Study key: [1]McKetin et al. (2006); [2]Dawe et al. (2013); Lapworth et al. (2009); [3]McKetin et al. (2010); [4]McKetin et al. (2013); McKetin et al. (2016); [5]Hides et al. (2015); [6]Chen et al. (2003, 2005, 2007), Lin et al. (2004); [7]Glasner-Edwards et al. (2008); Zweben et al. (2004); [8]Sulaiman et al. (2014); [9]Ding et al. (2014); [10]Rognli et al. (2014); [11]Kalayasiri et al. (2009, 2014); [12]Smith et al. (2009); [13]Salo et al. (2013).
[b]Outcome-level quality of evidence was very low–low for all risk factors except MA frequency based on the GRADE criteria.

reported hospitalisation for substance-induced psychotic disorder (Rognli et al., 2014).

Other drug use. Use of alcohol and other non-stimulant drugs was associated with an increased risk of MAP in five studies (Chen et al., 2003; Kalayasiri et al., 2009; McKetin et al., 2013; Smith et al., 2009; Sulaiman et al., 2014). In particular, co-morbid alcohol and cannabis use or dependence were associated with MAP in three studies (Chen et al., 2003; Kalayasiri et al., 2009; McKetin et al., 2013). One study did not find an association between alcohol dependence and MAP, but had a sample recruited from inpatient psychiatric and rehabilitation settings in a Muslim country, where disclosure of alcohol use may have been less socially acceptable compared to other settings (Sulaiman et al., 2014). There were inconsistent results on the association between a lifetime history of other drug use and MAP.

Psychiatric co-morbidity. Four studies assessed co-morbid affective and anxiety disorders and reported inconsistent results in terms of their association with psychosis (Chen et al., 2003; McKetin et al., 2006, 2016; Sulaiman et al., 2014). These studies did not distinguish between primary or secondary psychiatric co-morbidity in the context of active substance use.

Personality factors. One study suggested a higher incidence of premorbid schizoid or schizotypal personality traits in individuals with MAP (Chen et al., 2003). Four studies supported an association between the prevalence of current diagnoses of antisocial personality disorder or a history of conduct disorder and MAP (Chen et al., 2003; Kalayasiri et al., 2009; McKetin et al., 2016; Sulaiman et al., 2014).

Family history of psychosis or psychiatric illness. Family history was assessed in five studies (Chen et al., 2005; Hides et al., 2015; McKetin et al., 2016; Rognli et al., 2014; Salo et al., 2013). Among these, three found no significant association between family history of psychiatric illness and MAP (Hides et al., 2015; Rognli et al., 2014; Salo et al., 2013). One study that utilised a validated assessment tool, with collateral history from a family member, found that those with a family history of schizophrenia were five times more likely to have a lifetime history of substance-induced psychotic disorder (OR 5.4, 95% CI=[2.0, 14.7], $p<0.001$; Chen et al., 2003). One further study suggested an association between persistent (but not transient) current psychosis symptoms and a family history of psychotic illness (McKetin et al., 2016).

Trauma. Only one study examined the predictor of lifetime history of sexual or physical abuse and did not find any association between this and MAP (Rognli et al., 2014). One study examined the prevalence of adverse childhood experiences (ACEs) on the development of MAP and found that individuals with three or more adverse childhood experiences had a significantly higher risk of lifetime MAP (OR=4.5, 95% CI=[1.6, 12.6]; Ding et al., 2014). This study also found a graded relationship between the number of ACEs and psychosis that remained significant after controlling for sociodemographic variables, duration and frequency of drug use and dependence and other drug use (Ding et al., 2014).

Risk of bias across studies. The quality of the evidence for each predictor as a correlate of MAP was synthesised across studies using the GRADE approach (Atkins et al., 2004; Guyatt et al., 2008) and was found to be low–very low across almost all predictors as a result of an observational study design; unexplained heterogeneity; inconsistency of evidence across studies and multiple sources of bias (Table 2). The only outcome for which there was a

moderate level of evidence was frequency of MA use, with evidence of moderate–large effect sizes (Ding et al., 2014; Kalayasiri et al., 2009, 2014; McKetin et al., 2006, 2013) and a dose–response relationship between MA frequency and odds of psychosis symptoms (McKetin et al., 2013).

Discussion

This is the first comprehensive review to examine correlates of psychosis among people who use illicit MA. We found moderate evidence that more frequent MA use was associated with a dose-related increase in the likelihood of psychotic symptoms. There was also consistent evidence that other indices of MA use (quantity of MA use and greater severity of MA dependence) were associated with greater odds of psychotic symptoms. The frequency of use and severity of dependence have been shown to be highly correlated in amphetamine use populations (Gossop et al., 1995), and so, taken together, this adds to the concept that greater use of the drug results in a greater likelihood of psychosis. Polydrug use, particularly alcohol dependence and frequent cannabis use, was also associated with MAP. Sociodemographic factors, such as age, gender and employment status, were not associated with psychosis risk among people who use MA.

Strengths and limitations of this review

This review represents the most comprehensive, rigorous and up-to-date perspective on the evidence for correlates of MAP. The use of a priori criteria, systematic searching (in any language) and independent quality assessments by two co-authors are key strengths of this study, in comparison to previous reviews (Bramness et al., 2012; Bramness and Rognli, 2016). Methodological limitations, however, include the lack of validation of the adapted version of the Newcastle–Ottawa Scale (Wells et al., 2011) used to assess individual study quality and the inability to pool results due to both statistical and qualitative heterogeneity, with outcome-level quality of evidence assessed qualitatively with reference to the GRADE approach.

A key issue with the literature in this area relates to the variability in measurement of psychosis. The search strategy for this review was intentionally broad in order to capture any relevant studies. However, heterogeneity and inconsistency in the measures used to assess the outcome of psychosis prevented any meta-analysis in this review. Less than half of the studies included in this review measured current psychosis symptoms against current MA use (Hides et al., 2015; Lapworth et al., 2009; McKetin et al., 2006, 2010, 2013). In comparison, eight other studies (Chen et al., 2003; Ding et al., 2014; Kalayasiri et al., 2009; Rognli et al., 2014; Salo et al., 2013; Smith et al., 2009; Sulaiman et al., 2014; Zweben et al., 2004) reported lifetime MA–induced psychotic disorders or symptoms as their primary outcome measure and related this to MA use at the time of the study, such that MA use may have occurred at a different time from psychosis outcomes. A further issue arises from the difference in measuring psychotic symptoms versus a disorder and speaks to the inherent difficulties in comparing outcomes based on dimensional, categorical or clinical measures of a syndrome. This is paralleled by a shift in the recent conceptualisation of psychosis, from categorical clinical diagnoses to a more transdiagnostic approach, reflecting a range of symptoms that may relate to different trajectories and disorders (Lappin et al., 2016). In this context, broader definitions of psychoses, such as those used in some of the included studies (Lapworth et al., 2009; McKetin et al., 2006, 2010; 2013), do have the advantage of capturing the full spectrum of psychotic symptoms, even if this does not equate to a clinical diagnosis.

A further limitation of this review relates to its reliance on observational studies, most of which were cross-sectional, and therefore clearly limited in terms of ability to test causal relationships and predictive associations. This is a common problem in dual-diagnosis research, particularly when studying early-onset progressive disorders such as chronic psychotic illness, where it can be difficult to identify whether drug exposure or other risk factors predate the onset of the illness and to account for a range of potential measured and unmeasured confounding (Kendler, 2017). On one hand, there is evidence that MA can trigger psychosis in experimental settings (Angrist and Gershon, 1970; Bell, 1973), and psychosis is a recognised adverse effect of psychostimulant medication for treatment of attention deficit hyperactivity disorder (Ross, 2006). However, this evidence does not translate directly to the use of illicit MA in non-experimental settings, as other factors (for instance, related to the drug, the individual or the environment) may moderate this relationship. A further factor to consider when examining evidence from observational studies is whether the outcome of interest was present in the cohort at baseline – seven of the included studies failed to exclude individuals with primary psychotic disorders from their samples (Dawe et al., 2013; Ding et al., 2014; Kalayasiri et al., 2009, 2014; Lapworth et al., 2009; Rognli et al., 2014; Smith et al., 2009). Thus, while the frequency and amount of MA use and severity of dependence were shown to be consistently associated with psychotic symptoms, the literature presented in this review is insufficient to support a causal association.

Many of the included studies were conducted in mixed substance-using populations. In this review, we chose to include any studies that specifically reported outcomes for individuals citing MA or amphetamine as their primary drug of concern. This definition included populations that were purposively recruited on the basis of MA use, as well as mixed use populations where results were specifically presented for individuals nominating MA as their drug of choice. This is a typical approach in the substance use

literature, given that poly-drug use is the norm rather than the exception in most illicit drug use populations, but this does give rise to confounding related to poly-drug use and to the differences in lifestyle and psychosocial circumstances that may accompany poly-drug use patterns. This is particularly salient when studying the phenomenon of psychosis, with clear evidence that a range of other drugs have the potential to precipitate or perpetuate psychosis, such as other stimulants or cannabis (Murray et al., 2013). Only six of the included studies in this review reported adjusted outcomes that controlled for this confounding factor, and this remains a significant limitation of the existing evidence in this area (Ding et al., 2014; McKetin et al., 2006, 2010, 2013, 2016; Sulaiman et al., 2014).

MA-associated psychosis has been proposed by some authors as a potential model for schizophrenia (Bousman et al., 2011; Hermens et al., 2009; Yui et al., 2000); the two disorders have very similar acute clinical syndromes, and studies suggest that up to 30% of individuals with a history of MAP have been found to transition to persistent psychotic illness in longitudinal studies (Niemi-Pynttäri et al., 2013). If this is valid, and MAP is part of the same phenomenon as primary psychotic disorders such as schizophrenia, it is conceivable that established risk factors for schizophrenia can be expected to also raise the risk of psychosis in MA users. However, there is insufficient evidence to support this at present. Putative risk factors for schizophrenia (Tsuang et al., 2001; Van Os et al., 2010) including genes and environmental factors (Tsuang et al., 2001; Van Os et al., 2010) such as maternal nutrition (Brown and Susser, 2002), paternal age (Malaspina et al., 2001), migration (Cantor-Graae and Selten, 2005), urbanicity or childhood adversity and trauma (Matheson et al., 2013) have not yet been shown to be relevant in the aetiology of MAP. Therefore, the extent to which the aetiological pathways of MAP and schizophrenia overlap remains unclear.

Implications for future research

The main limitation of existing research arises from the heterogeneity in study designs, study populations and the measures used for psychosis. Future studies examining this question should aim to exclude individuals with primary psychotic illness at baseline and should involve validated and contemporaneous assessment of MA and other substance use with measures of psychosis, such as the Timeline Followback method (Sobell and Sobell, 1992). Analysis in studies should, at a minimum, seek to measure and control for confounding factors such as other drug use.

In order to strengthen our understanding of the risk factors for psychosis among people who use MA, more data are needed on factors that have only been studied previously a small number of studies, including family history of psychotic disorders or a history of childhood stress or trauma. Similarly, no studies have investigated protective factors in MA psychosis. It is unclear what role familial support or social capital may play in increasing the resilience of an individual using MA.

Existing research has also frequently been based on restricted sample populations such as injecting drug users or in drug rehabilitation or incarceration settings. These settings may not be truly representative of adults who use illicit MAs, and future studies should seek to recruit both individuals from community and treatment seeking settings with a wide range of MA use histories and trajectories. Finally, while we included a number of longitudinal studies in our review, we did not specifically focus on factors related to the transition to chronic psychotic disorders. This is a key question that could potentially be answered by future reviews.

Implications for clinicians

The results of this review suggest that MA-related factors, such as frequency and quantity of use and severity of MA dependence, have the most consistent evidence as correlates of MAP. This highlights the need for clinicians to specifically obtain a detailed history of recent MA use amounts and patterns of use from individuals in both mental health and substance use treatment settings; while this may seem obvious, this point is worth labouring, as accurate assessment may be hampered by some mental health clinicians' lack of confidence or training in assessing co-existing substance use disorders (De Crespigny et al., 2015). Similarly, harm-reduction messages targeted at this population should emphasise the association between MA use patterns and psychosis and should be aimed at helping non-treatment-seeking individuals minimise their risk of developing this significant adverse effect.

Based on the results of this review, individuals with high dose use of MA should be recognised as a high-risk group for psychosis. The case for an early intervention approach is particularly salient for MA-using individuals, as efforts made to engage them in treatment earlier in their use trajectory may prevent progression to chronic and disabling illness (Lappin et al., 2016). Such individuals presenting either to mental health or alcohol and other drug clinical services may warrant higher intensity, targeted approaches to minimise the risk of psychosis. This has implications for service delivery, necessitating a better resourced, integrated and longer term dual-diagnosis model of care in order to adequately address the needs and risks of this population (Lappin et al., 2016).

Conclusion

Among MA users without a primary psychotic disorder, the most consistent predictors of psychotic symptoms are frequency and quantity of MA use and the presence of dependence features. Further research is required to conclusively

determine whether other factors, such as trauma, family history of psychotic illness and other substance use are predictive of MA-associated psychosis. The findings of this review highlight the need for targeted assessment and treatment of MA use in individuals presenting with psychosis.

Declaration of Conflicting Interests

Dan Lubman has provided consultancy advice to Lundbeck and Indivior and has received travel support and speaker honoraria from Astra Zeneca, Bristol Myers Squibb, Janssen, Lundbeck and Servier.

Funding

This research was supported by the Australian National Health and Medical Research Council (NHMRC) postgraduate scholarship (Grant 1093778) which provided a stipend to the primary author during PhD candidature.

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6.2 Discussion and Summary

This study demonstrated that the key correlates of methamphetamine-associated psychosis are methamphetamine use variables (frequency of use and severity of dependence), whereas there is limited evidence for non-drug related risk factors. Many of the strengths and limitations of the study, as discussed in the manuscript, relate to systematic review methodology in general. While the wide variety of definitions and measurement of psychosis outcomes impacted on the ability to conduct a meta-analysis in this study, this narrative synthesis remains the only review in this area to utilize a systematic approach to consolidating evidence on MAP. The results of the review highlight a gap in the extant literature on non-drug markers of psychosis-proneness in MAP,

In the following chapters (Chapters 7-9), a series of papers investigate whether cognitive factors can be considered a potentially useful correlate of MAP.

7. Chapter 7: Cognitive and Social Cognitive Correlates of MAP

7.1. Introduction

Methamphetamine (MA) is a potent and addictive synthetic stimulant drug, the second most commonly used illicit drug worldwide (3) and related to a growing burden of mental illness (6). MA and amphetamine use have been associated with psychotic symptoms in healthy subjects in experimental studies (1), during acute intoxication with illicit use (145, 146), and in persistent forms of psychosis resembling chronic primary psychotic disorder (36, 139, 145). Seen in between 20-60% of individuals who use the drug regularly (145), methamphetamine-associated psychosis (MAP) contributes to a significant burden on acute health and psychiatric inpatient services (7, 147). While most individuals with MAP present with brief and transient psychotic symptoms, between 19-33% of people hospitalized for stimulant-induced psychosis have persistent symptoms that are later diagnosed as primary psychotic disorders (148). Although there is a growing body of evidence characterizing the MAP syndrome, there is currently little evidence to inform a comprehensive understanding of correlates of psychotic symptoms in MAP.

There is emerging evidence that cognitive factors may be useful predictors of persistent versus acute MAP (139, 140). Chen and colleagues' study identified impairments in attention, verbal learning and memory, and executive function and decision making in individuals with persistent MAP. Importantly, the persistent MAP group had a similar cognitive deficit profile to a chronic schizophrenia comparison group, with poorer performance compared to both healthy controls or people who used methamphetamine regularly and did not have psychosis (139). To date, only two studies have assessed cognition in acute MAP, and both have found impairments in these cohorts compared to healthy controls, with similar cognitive performance in the MAP group compared to individuals with schizophrenia (137, 138). Notably, impairments in similar cognitive domains, particularly verbal memory, have also been demonstrated in studies investigating first episode psychosis (149), contributing to a growing body of evidence pointing to commonalities in the process of psychosis in MAP and primary psychotic disorders (145). However, whether the findings in MAP populations relate to drug use characteristics, such as the amount and pattern of methamphetamine use, or whether they reflect an individual-level propensity to developing psychotic symptoms with methamphetamine use remains unclear. There is a need to replicate the results of these studies adjusting for these factors, and to extend this to other domains known to be impaired in primary psychosis, such as social cognition.

To our knowledge, no previous studies have examined social cognition in the study of any type of substance-associated psychosis. Impairment in social cognition is a robust finding across a range of psychotic disorders (118). Deficits in facial emotion recognition (FER), a specific domain of social cognition, have been consistently found in both ultra-high risk and first episode psychosis populations (150), suggesting these impairments may be pre-existing, and independent of the stage of psychotic illness. Although further research is required to clarify the utility of social cognition as a marker of transition to persistent primary psychosis (134, 150), it nevertheless represents a promising therapeutic target in high risk and established psychosis populations in terms of functional outcomes (151, 152).

In contrast, studies of stimulant dependence have examined associations between FER and substance use but have not explored links with psychotic symptoms. To date, only four studies have focused specifically on FER in methamphetamine dependence, of which three identified impairments in FER in comparison with healthy control participants (133-135, 153). However, the findings were limited by sample size with three of these studies recruiting under 30 participants; and they lacked generalizability as they were conducted in abstinent participants in early recovery. Furthermore, none of these studies assessed symptoms of psychosis or other mental health problems, and therefore any differences between stimulant-dependent and non-drug using groups have been attributed to stimulant use alone. This is a key gap in the literature, and the nature and extent of the relationship between psychotic symptoms and social cognition in this population remains unknown.

Further, a key diagnostic dilemma for clinicians in these settings is distinguishing between symptoms that are methamphetamine-induced or related to an underlying primary psychotic disorder. Operational criteria are limited in their ability to distinguish between a substance-induced psychotic episode and primary psychotic illness (33), and the presenting syndrome of methamphetamine psychosis is heterogenous. For instance, whilst the majority of people present with acute symptoms of suspiciousness and auditory hallucinations, negative and first rank symptoms are observed in a minority(89, 90). Importantly, there is emerging evidence to suggest that particular symptom subtypes reported in the first episode of methamphetamine psychosis relate to trajectory to persistent illness(85). This evidence largely comes from self-report and retrospective symptom assessment, however, and is susceptible to inherent biases. In contrast, measurement of cognitive correlates of MAP may present an alternative method of providing useful information regarding presenting profiles(139). However, there is relatively little literature investigating whether

cognitive correlates vary with symptom type.

As such, we sought to investigate the relationship between cognition (neurocognition and FER), drug use patterns and psychotic symptoms in a population of adults who used methamphetamine regularly. The primary hypothesis of this study was that positive psychotic symptoms would be associated with impairments in cognition (FER, verbal memory, executive function and decision-making) in people who used methamphetamine regularly, following adjustment for severity of methamphetamine use, and a range of confounding factors previously identified to impact on the relationship between cognition and psychosis, including age, gender and IQ.

Finally, we sought to investigate whether impairments in cognition varied based on predominant presenting positive psychotic symptom typology. We hypothesized that specific symptom types would predict different profiles of cognitive impairment.

7.2. METHODS

7.2.1. SETTING AND PARTICIPANTS

Participants were 103 adults residing in metropolitan Melbourne, Australia, who reported using methamphetamine at least weekly in the past month. Participants were recruited between March 2015 to February 2017 from both public and private residential treatment facilities, and from community settings, via advertisements in free-press magazines, and needle syringe exchange programmes.

Inclusion criteria included (i) aged 18 years or older, (ii) identifying methamphetamine as primary drug of concern (iii) regular methamphetamine use defined as at least once a week in the past month, (iv) not currently dependent on any drugs other than methamphetamine, cannabis, alcohol or nicotine, (v) having no previous diagnoses of schizophrenia, bipolar disorder or other chronic psychotic illness, (vi) having a minimum IQ of 70 and (vii) having no history of loss of consciousness for more than 30 minutes, HIV, epilepsy, or any central neurological illness.

The Structured Clinical Interview for DSM-IV TR (SCID-I/P; (30)) was used to diagnose a lifetime history of schizophrenia or bipolar disorder and evaluate current substance dependence diagnoses. A face-to-face 1.5-hour interview was carried out by a researcher at a mutually convenient time and quiet location.

Participants were requested to abstain from using alcohol or any drugs on the day of the assessment. Those who were eligible to participate completed informed consent and were reimbursed AU$30 for their time and expenses. The study received ethics approval from all treatment sites and from Monash University Human Research Ethics Committee (CF15/40- 2015000222).

7.2.2. Measures

7.2.2.1. Psychosis

Past month positive psychotic symptoms were assessed using the Brief Psychiatric Rating Scale (BPRS; (154)), a measure of psychosis used in previous studies of methamphetamine dependent populations, with high inter-rater reliability reported in original studies (r= 0.67-0.88)(40). The dependent variable was the total score of the positive symptom items of suspiciousness, hallucinations and unusual thought content (ranging from 3-21) (154, 155). In addition, the score for each individual positive symptom item was used to define predominant symptom typology. All research interviews were conducted by postgraduate researchers with clinical experience who had completed training in the BPRS.

7.2.2.2. Neuropsychological test battery

The neuropsychological test battery targeted cognitive domains associated with psychostimulant use (127) and deficits in emotion recognition associated with primary psychotic disorders (156, 157). The following tasks were administered in a set order and nested within the structured interview.

i. IQ: The Vocabulary and Matrix Reasoning subscales of the Wechsler Abbreviated Scale of Intelligence (WASI-II; (158)) was used to estimate current full IQ.
ii. Ekman Faces Test (EFT): a computerised task that assesses recognition of facial emotional expressions. A series of 60 faces portraying basic emotions are presented, using stimuli from the Facial Expressions of Emotion: Stimuli and Tests (FEEST) (159). Faces depicted the following emotions, anger, fear, disgust, happiness, sadness, surprise; with 10 faces for each of the 6 emotions. The dependent variables for this task were the total number of correct identifications (ranging 0-60), as well as the number of correct identifications for each discrete emotion (scored 0-10 for each emotion).
iii. Iowa Gambling Task (IGT): a computerised task evaluating reward and punishment-based decision-making (160). The task instructs participants to try and win as much money as possible by making 100 selections of cards from four decks (A, B, C, D). Two of the decks (A and B) result in

high immediate gains but in the long term will take more money than they give and can be considered 'disadvantageous'. In contrast, two decks (C and D) have low immediate gains but will yield more money than is taken and can be considered 'advantageous'. The dependent variable was the net score, calculated by subtracting the number of disadvantageous choices (decks A + B) from the number of advantageous choices (decks C+D) for each block of 20 trials.

iv. Delay Discounting Task (DDT): a measure of impulsivity in decision-making, examining the outcome of 27 choices between smaller immediate rewards versus larger delayed rewards, based on the Kirby Monetary Choice Questionnaire (161), with the main dependent variable calculated as the *k* score based on methods detailed by Kirby and colleagues, with higher *k* scores indicating higher levels of impulsivity(161).

v. The Hopkins Verbal Learning Test- Revised (HVLT-R)(162): a measure of verbal learning and memory, with assessment of both recognition and recall. Participants are read a list of 12 words and advised to recall as many as they can; this trial is repeated two times (total of 3 trials). Delayed recall is assessed at 20-25 minutes. Participants are then read a list of 24 words and asked to identify words from the original list (recognition). The main dependent variable for this study was based on delayed recall.

7.2.2.3. METHAMPHETAMINE USE

Frequency of methamphetamine use in the past month was assessed using the Timeline Followback (TLFB). The TLFB is a validated measure of substance use and shows 88% sensitivity, 96% specificity, and a 95% hit-rate and 0.77 test-retest agreement, for the use of amphetamines in the past 30 days (163).

7.2.2.4. OTHER DRUG USE MEASURES

Participants were excluded if they were dependent on drugs other than methamphetamine, nicotine, alcohol or cannabis based on DSM-IV diagnoses (30). The severity of dependence on methamphetamine, cannabis and alcohol was measured using the Severity of Dependence Scale (164). This is a five-item measure with responses rated on a four- point Likert scale (0-3), and established cut-offs of >=4, and >=3 and >=3 were used that correlated with DSM-IV diagnoses of methamphetamine (165), cannabis (166) and alcohol (167) dependence respectively. The dependent variable was the severity of dependence (SDS) score ranging from 0-15 (low severity to high severity of dependence). A structured questionnaire also assessed (i) main route of methamphetamine use (ii) amount of methamphetamine use per occasion (iii) age of first methamphetamine use and (iv) years of methamphetamine use.

7.3. STATISTICAL ANALYSES

Firstly, we sought to identify confounding variables for the relationship between (i) cognition and psychotic symptoms and (ii) cognition and methamphetamine use. We investigated associations between (i) past month psychotic symptoms (total BPRS positive symptom score) and (ii) methamphetamine use variables (severity of dependence, frequency of use and age of onset of use), and demographic, clinical and cognitive measures using Spearman correlations to test bi-variate correlations on non-parametric data and Mann-Whitney U-tests for categorical data. In addition, we investigated correlations between all dependent variables to inform potential confounders, and to understand any associations between these variables. This exploratory analysis was undertaken without Bonferroni correction for multiple tests of association as we aimed to identify any possible confounders to include in the main regression model

To address the main hypothesis, we performed a multiple regression analysis using the total positive symptoms score as the outcome measure, and total emotion recognition score as the predictor variable, adjusting for confounding variables, based on variables found to have a significant correlation with psychotic symptoms in the analysis above (severity of methamphetamine dependence, IQ). Truncated negative binomial regression was used due to the nature of the positive symptom score as an over dispersed count variable with a greater variance than mean (Variance 9.537 > Mean 5.951) and a minimum BPRS score of 3 (168), with reporting of incidence rate ratios (IRR).

We also investigated the relationship between positive psychotic symptom domains and discrete recognition of facial emotions using a truncated negative binomial regression method to model psychotic symptoms, as an over-dispersed count outcome (168), reporting the incidence rate ratio (IRR). Adjustment was made for the following potential confounds based on previous literature on social cognition in methamphetamine dependence(127), including age, gender, years of education and severity of methamphetamine, alcohol and cannabis dependence.

All data analyses were conducted using Stata Version 15.0 (Statacorp LP, College Station, TX, USA), with a statistical significance level of $p < 0.05$ and 2-tailed tests of significance.

7.4. Results

7.4.1. Participant characteristics

Participant characteristics are presented in Table 1. Participants (N = 103) had a mean (SD) age of 32.5 (9.5) years, the majority were men and unemployed (75% each). The mean (SD) duration of methamphetamine use was 7 years, participants had used on a median (IQR) of 28 days (13-31) in the past month and 91% were dependent on methamphetamine. A minority of participants were being prescribed psychotropic medication, including anti-depressants (12%), benzodiazepines (3%), or anti-psychotics (6%). The mean total positive symptom score was 5.95 (SD 3.09, range 3-16)

7.4.2. Relationship between methamphetamine use and psychosis

As can be seen in Table 1, methamphetamine dependence, and the severity of methamphetamine dependence were correlated with the total positive psychotic score.

Table 1 Sample characteristics and their association with positive psychotic symptom score

Variable	Whole sample (n=103) Mean (SD) or N (%)	Test statistic[a]	P value
Sociodemographic			
Age (years)	32.5 (8.5)	-0.07	0.543
Male	77 (75)	881.0	0.356
Unemployed	76 (75)	817.5	0.291
IQ (WASI FSIQ[b])	96.8 (1.1)	-0.13	0.190
Methamphetamine use & other drug use			
Frequency of MA[c] use in the past month (days)	22.0 (9.6)	0.12	0.270
Age first MA use (years)	24.3 (8.3)	0.04	0.717
Injecting MA	30 (29)	4.42	0.219
MA dependent	94 (91)	120.5	<0.001
MA SDS[d] score	10.4 (3.7)	0.23	0.029
Cannabis dependence	24 (23)	795.5	0.228
Alcohol dependence	7 (7)	302.0	0.652
Neurocognition & social cognition			
Verbal memory (HVLT-R[e] delayed recall)	8.5 (2.4)	-0.02	0.851
IGT[f] net score	1.9 (24.2)	-0.17	0.099
DDT[g] k score	0.2 (0.1)	-0.08	0.427
Ekman's total score	45.0 (6.9)	-0.29	0.005

a: Test statistic- Spearman's rho for continuous non-parametric data, Mann-Whitney U-test for categorical data b: WASI FSIQ- Wechsler Abbreviated Scale of Intelligence Full Scale IQ c: MA- methamphetamine d: SDS- Severity of Dependence Scale e: HVLT-R- Hopkins Verbal Learning Test- Revised f: IGT- Iowa Gambling Task g: DDT- Delay Discounting Task

7.4.3. RELATIONSHIP BETWEEN METHAMPHETAMINE USE AND COGNITION

Cognitive performance (IGT, DDT, HVLT-R delayed recall) did not correlate with any methamphetamine use variables. FER was positively correlated with the age of onset of methamphetamine use (see Table 2).

Table 2 Sample characteristics and their association with methamphetamine use variables

Variable	Severity of methamphetamine dependence		Frequency		Age of onset	
	Test statistic[a]	P value	Test statistic[a]	P value	Test statistic[a]	P value
Sociodemographic						
Age	0.08	0.482	0.08	0.513	0.66	<0.01
Male gender	-0.02	0.833	-0.11	0.326	0.01	0.924
Unemployment	0.19	0.100	0.25	0.026	0.24	0.050
Neurocognition & social cognition						
IQ	-0.06	0.545	-0.01	0.923	0.09	0.439
Verbal memory (HVLT-R[b] Delayed)	-0.11	0.322	0.05	0.666	0.12	0.310
IGT[c] net score	-0.12	0.292	-0.02	0.832	0.13	0.269
DDT[d] k score	0.11	0.331	0.06	0.602	-0.16	0.166
Ekman's total score	-0.07	0.531	0.01	0.944	0.24	0.040

a: Teststatistic-Spearman'srhoforcontinuousnon-parametricdata, Mann-WhitneyU-testfor categorical data b: HVLT-R- Hopkins Verbal Learning Test- Revised c: IGT- Iowa Gambling Task d: DDT- Delay Discounting Task

7.4.4. OTHER CORRELATED VARIABLES

A correlation table of all dependent variables (Table 3) identified correlations between IQ and verbal memory ($p<0.01$) and Ekman's total score (facial emotion recognition performance) ($p<0.01$).

Table 3 Correlation Table for all dependent variables

	Age	Gender (male)	Unemployed	IQ	Frequency of MA use	Age onset (MA)	Route of use (injecting	MA severity of dependence (SDS)	Cannabis dependence	Alcohol dependence	Verbal memory (delayed recall)	IGT net score	DDT k score	Ekman's total score	BPRS Pos Total score
Age	1.00	0.02 (0.83)	0.10 (0.35)	-0.03 (0.80)	-0.06 (1.00)	**0.67 (0.00)**	**-0.34 (0.00)**	0.01 (0.89)	-0.03 (0.76)	0.06 (0.58)	-0.18 (0.08)	0.13 (0.23)	-0.21 (0.04)	-0.00 (0.97)	-0.03 (1.00)
Gender (male)	0.02 (0.83)	1.00	-0.07 (0.52)	0.02 (0.87)	-0.15 (0.15)	0.01 (0.92)	-0.10 (0.34)	-0.06 (0.55)	-0.01 (0.93)	0.05 (0.67)	0.12 (0.24)	-0.13 (0.19)	-0.07 (0.46)	0.18 (0.08)	-0.14 (0.18)
Unemployed	0.10 (0.35)	-0.07 (0.52)	1.00	0.12 (0.25)	**0.25 (0.02)**	**0.23 (0.05)**	**0.21 (0.05)**	**0.26 (0.01)**	-0.01 (0.93)	-0.15 (0.14)	0.04 (0.69)	-0.01 (0.90)	-0.07 (0.48)	0.17 (0.10)	-0.13 (0.21)
IQ	-0.03 (0.80)	0.02 (0.87)	0.12 (0.25)	1.00	0.06 (0.60)	0.11 (0.35)	-0.03 (0.76)	-0.05 (0.65)	-0.15 (0.15)	-0.05 (0.64)	**0.40 (0.00)**	0.02 (0.82)	-0.11 (0.30)	**0.60 (0.00)**	-0.10 (0.32)
Frequency of MA use	- 0.06 (0.59)	-0.15 (0.15)	**0.25 (0.02)**	0.06 (0.60)	1.00	0.02 (0.83)	0.19 (0.07)	**0.37 (0.00)**	-0.08 (0.47)	0.02 (0.89)	0.06 (0.56)	-0.12 (0.25)	0.05 (0.64)	0.02 (0.88)	0.13 (0.22)
Age onset (MA)	**0.67 (0.00)**	0.01 (0.92)	**0.23 (0.05)**	0.11 (0.35)	0.02 (0.83)	1.00	-0.18 (0.11)	0.03 (0.79)	0.04 (0.74)	-0.11 (0.32)	0.12 (0.30)	0.14 (0.22)	-0.15 (0.18)	**0.24 (0.04)**	0.02 (0.85)
Route of use (injecting)	**-0.34 (0.00)**	-0.10 (0.34)	**0.21 (0.05)**	-0.03 (0.76)	0.19 (0.07)	-0.18 (0.11)	1.00	**0.23 (0.03)**	0.02 (0.88)	**-0.22 (0.03)**	0.05 (0.64)	-0.02 (0.85)	**0.20 (0.05)**	0.08 (0.43)	-0.09 (0.40)
MA severity of dependence (SDS)	0.01 (0.89)	-0.06 (0.55)	**0.26 (0.01)**	-0.05 (0.65)	**0.37 (0.00)**	0.03 (0.79)	**0.23 (0.03)**	1.00	-0.01 (0.93)	0.00 (0.98)	-0.07 (0.53)	-0.15 (0.15)	0.18 (0.08)	-0.07 (0.48)	**0.20 (0.05)**
Cannabis dependence	-0.03 (0.76)	-0.01 (0.93)	-0.01 (0.93)	-0.15 (0.15)	-0.08 (0.47)	0.04 (0.74)	0.02 (0.88)	-0.01 (0.93)	1.00	0.08 (0.47)	-0.17 (0.11)	-0.04 (0.73)	0.14 (0.19)	-0.02 (0.83)	0.08 (0.47)
Alcohol dependence	0.06 (0.58)	0.05 (0.67)	-0.15 (0.14)	-0.05 (0.64)	0.02 (0.89)	-0.11 (0.32)	**-0.22 (0.03)**	0.00 (0.98)	0.08 (0.47)	1.00	-0.20 (0.06)	-0.01 (0.91)	0.09 (0.40)	-0.03 (0.84)	-0.08 (0.47)
Verbal memory (delayed recall)	-0.18 (0.08)	0.12 (0.24)	0.04 (0.69)	**0.40 (0.00)**	0.06 (0.56)	0.12 (0.30)	0.05 (0.64)	-0.07 (0.53)	-0.17 (0.11)	-0.20 (0.06)	1.00	0.12 (0.27)	-0.14 (0.19)	**0.37 (0.00)**	-0.01 (0.92)
IGT net score	0.13 (0.23)	-0.13 (0.19)	-0.01 (0.90)	0.02 (0.82)	-0.12 (0.25)	0.14 (0.22)	-0.02 (0.85)	-0.15 (0.15)	-0.04 (0.73)	-0.01 (0.91)	0.12 (0.27)	1.00	0.08 (0.44)	0.05 (0.66)	-0.17 (0.11)
DDT k score	-0.21 (0.04)	-0.07 (0.46)	-0.07 (0.48)	-0.11 (0.30)	0.05 (0.64)	-0.15 (0.18)	**0.20 (0.05)**	0.18 (0.08)	0.14 (0.19)	0.09 (0.40)	-0.14 (0.19)	0.08 (0.44)	1.00	-0.01 (0.95)	-0.07 (0.50)
Ekman's total score	-0.00 (0.97)	0.18 (0.08)	0.17 (0.10)	**0.60 (0.00)**	0.02 (0.88)	**0.24 (0.04)**	0.08 (0.43)	-0.07 (0.48)	-0.02 (0.83)	-0.03 (0.84)	**0.37 (0.00)**	0.05 (0.66)	-0.01 (0.95)	1.00	**-0.30 (0.00)**
BPRS Pos total score	-0.03 (1.00)	-0.14 (0.18)	-0.13 (0.21)	-0.10 (0.32)	0.13 (0.22)	0.02 (0.85)	-0.09 (0.40)	**0.20 (0.05)**	0.08 (0.47)	-0.08 (0.47)	-0.01 (0.92)	-0.17 (0.11)	-0.07 (0.50)	**-0.30 (0.00)**	1.00

7.4.5. RELATIONSHIP BETWEEN COGNITION AND PSYCHOSIS

FER was significantly associated with the positive symptom score, but the other cognitive domains assessed (IGT, DDT, HVLT-R delayed recall) were not (see Table 1; 3). In the negative binomial regression model, emotion recognition (Ekman total score) remained significantly associated with the total positive symptom score after adjusting for severity of methamphetamine dependence and IQ (unadjusted IRR= 0.96 (95% CI 0.93-0.99); adjusted IRR 0.96 (95% CI 0.93-0.99)) (Table 4).

Table 4 Multivariate regression model predicting total BPRS positive symptom score

Predictors	**IRR[a]**	**SE**	**95% CI**	**P value**
IQ	1.01	0.01	0.99-1.02	0.546
Severity of MA dependence	1.03	0.03	0.98- 1.08	0.258
Ekman's Total score	0.96	0.02	0.94- 0.99	0.018
Full model	LR chi^2 = 8.90, Pseudo R^2 = 0.019, Prob> chi^2 = 0.031			

a: IRR Incidence rate ratio

7.4.6. RELATIONSHIP BETWEEN POSITIVE PSYCHOTIC SYMPTOM TYPOLOGY AND RECOGNITION OF FACIAL EMOTIONS

The mean score for suspiciousness was the highest (M=2.19, SD 1.29), followed by hallucinations (M= 2.14, SD 1.36) and unusual thought content (M=1.61, SD 1.13).

The total emotion recognition score was significantly associated with past-month suspiciousness (p=0.014) but not hallucinations or unusual thought content. Suspiciousness was also associated with poorer recognition of disgust (IRR=0.901, p=0.011), while hallucinations were associated with poorer recognition of anger (IRR=0.887, p=0.036). Following adjustment (for age, gender, years of education, severity of methamphetamine, alcohol and cannabis dependence) there was only a significant association between past month suspiciousness and the number of correct identifications of disgust (IRR=0.924 (p=0.047)) (Table 5). There were no other significant associations between positive psychotic symptom domains and recognition of discrete emotions.

Table 5 Association between recognition of discrete emotions and positive psychotic symptoms

Variable	Unadjusted			Adjusted*		
	Suspiciousness IRR (p-value)	Hallucinations IRR (p-value)	Unusual Thought Content IRR (p-value)	Suspiciousness IRR (p-value)	Hallucinations IRR (p-value)	Unusual Thought content IRR (p-value)
Ekman Total Score	**0.970 (0.014)**	0.969 (0.065)	0.928 (0.066)	0.980 (0.114)		
Ekman- Anger	0.938 (0.187)	**0.887 (0.036)**	0.812 (0.073)		0.950 (0.342)	
Ekman- Disgust	**0.901 (0.011)**	0.921 (0.144)	0.901 (0.348)	**0.924 (0.047)**		
Ekman- Fear	0.937 (0.079)	0.930 (0.113)	0.920 (0.415)			
Ekman- Happiness	0.883 (0.144)	1.064 (0.637)	0.815 (0.409)			
Ekman- Sadness	0.940 (0.114)	0.935 (0.175)	0.859 (0.161)			
Ekman- Surprise	0.963 (0.529)	1.022 (0.772)	0.926 (0.634)			

IRR: Incidence Rate Ratio

*Adjusted for age, gender, education, severity methamphetamine, alcohol and cannabis dependence

7.5. DISCUSSION

This is the first study to demonstrate that methamphetamine-related psychotic symptoms (MAP) are associated with reduced facial emotion recognition (FER), supporting our primary hypothesis. This association remained statistically significant after adjusting for potential confounds (methamphetamine dependence and IQ). Importantly, we found that this impairment in FER, while correlated with age of onset of methamphetamine use, was not related to any other methamphetamine use variables. Contrary to our primary hypothesis, MAP was not associated with reduced performance in any other domains of cognitive function.

Our study provides limited evidence that particular positive psychotic symptom profiles present with different impairments in facial emotion recognition. Specifically, recognition of disgust appeared to be particularly impaired in people with suspiciousness, rather than other positive psychotic symptoms. Our findings are consistent with previous research that suggests that disgust

is particularly poorly recognized by individuals with schizophrenia, even at low or extreme emotional intensity(157, 169). Potential mechanisms for this specific deficit have included reduced activation of the interior insula(170, 171), and have also been observed in Parkinson's disease, with a possible association with dopamine dysfunction in the basal ganglia(172).

Given that we found limited evidence of an association between FER and methamphetamine use (age of onset, but not methamphetamine frequency or severity of dependence), our results do not support the concept of FER as a common correlate of both methamphetamine use and psychosis, but rather, are suggestive of FER as a specific correlate of psychotic symptoms in methamphetamine-using populations. This is compatible with the broader psychosis literature, where several studies have implicated impairments in FER as a trait phenomenon (173, 174), having been found in unaffected relatives (123), prior to first experiences of psychotic symptoms in high-risk populations (120, 150, 175), as well as remaining stable through the development and progression of a schizophrenic illness (173). Our results are also in line with other studies of MAP populations, that have demonstrated that while many individuals who use MA develop psychotic symptoms, a subset remain resilient regardless of level of use (145). However, given the cross-sectional nature of the current study, we were unable to make any inferences regarding causation or direction of association. Further prospective longitudinal research is required to clarify whether impairments in FER reflect neurocognitive vulnerability to MAP, and whether the presence of impaired FER predicts persistence of psychosis and transition to a primary psychotic disorder diagnosis.

We did not find an association between methamphetamine dependence and FER performance, which was in contrast to previous studies that did identify such an association (133, 134, 136). However, our sample size was substantially larger compared to previous studies (ranging from 12- 28 participants (133, 134, 136), and comprised participants with active methamphetamine use, as opposed to previous studies of FER in methamphetamine use, which were conducted in abstinent populations in early recovery {Henry, 2009 #204). Differences in the tasks used to measure FER may have also impacted on results, with previous studies measuring a narrower range of emotion recognition; for instance, recognition of only negative emotions such as fear and anger (136), or identification of four emotions (134) instead of six, as in the current study.

In terms of other domains of cognition, we did not find any association between performance on the cognitive tasks in this study and positive psychotic symptoms. Our limited neuropsychological battery, with only one task mapping to each of three cognitive domains, may be an explanation for this null finding. Alternatively, however, our results support the concept of distinct and separate processes underpinning emotion recognition and other cognitive domains (176). Previously, impairments in verbal memory and executive function have been reported in relation to MAP, but this has been in people with persistent MAP (139) rather than brief psychotic symptoms, as in our study. Other findings of cognitive impairment in MAP have been in small samples, and in comparison to healthy control participants or people with schizophrenia (137, 138).

The sample in this study had a homogenous pattern of methamphetamine use, which differed from

populations in previous studies. Most of the participants (55%) reported daily use of methamphetamine in the month prior to assessment. The limited variance in methamphetamine use frequency may account for the failure of this study to replicate an association between methamphetamine use frequency and likelihood of psychosis symptoms, as found by several other authors (5, 42, 47, 101). For instance, in comparison, a key study in this area was based on the MATES cohort recruited by McKetin and colleagues, which had only a third of the sample reporting frequency of use of more than 16 days in a month (42). In contrast, while the mean severity of methamphetamine dependence in this cohort was high (mean SDS 10.44) there was reasonable variation in SDS scores. This may explain the finding that severity of methamphetamine dependence had a significant association with positive psychosis symptoms, but methamphetamine use frequency did not. For this reason, we used severity of dependence as a proxy measure of methamphetamine use in the multivariate regression examining association between FER and psychotic symptoms.

Unexpectedly, we did not find any association between recognition of other emotions and specific symptoms subtypes. A potential explanation for this is that few participants in our study had severe psychotic symptoms. Previous studies have suggested that a symptom score of 4 or more on the BPRS can be considered "clinically significant"(42); in contrast, the mean scores of all positive psychotic symptoms in our study were less than 3. Overall, only 29% (n=30) of our sample scored 4 or more on any positive psychotic symptom. Our study therefore reflects mild or sub-threshold psychotic symptoms, and there may be potential associations between more specific psychotic symptom types and emotion recognition in clinical populations with more severe symptoms.

Strengths of this study included the use of a diagnostic interview (SCID I/P) to exclude pre-existing psychotic disorders, a key difference in comparison to a substantial number of studies in this area (177). We utilized the BPRS (154), a well validated psychotic symptom measure that has been widely used in other studies of methamphetamine-associated psychosis (42, 178) and primary psychotic disorders (155), allowing comparison of results. The primary outcome measure of psychosis was also based on rating of past month symptoms, with contemporaneous assessment of current substance use, enabling accurate correlation of the two domains. We conducted a dimensional assessment of past month psychotic symptoms, and this approach offered the benefit of investigating brief symptoms that are common in this population. This provides important insight, given the evidence that repeated experiences of psychotic symptoms in MAP may promote sensitisation, and the future development of a more sustained clinical psychotic syndrome (69). However, we did not distinguish between symptoms that were limited to periods of acute intoxication, or that were sustained for days to weeks from the last episode of use. Other studies of MAP have utilized a similar approach, examining experiences of symptoms rather than clinical syndromes (42, 48, 140, 179). Given the almost-daily patterns of methamphetamine use reported in our sample, and in other methamphetamine- dependent populations, we argue that it is virtually impossible to make this distinction in real-world settings.

This was a naturalistic study, with a pragmatic approach to sampling to enable translation to real-world treatment settings. Low proportions of the cohort were dependent on cannabis (23%) and alcohol (7%), and while this could have had potential effects on overall cognitive performance, this did not correlate with the primary outcome of psychosis. Less than a third (28%) of the population was prescribed any psychotropic drug (antidepressants, benzodiazepines, antipsychotics). This is generally much lower than that reported in other studies of cognition and substance use (137-139), and significantly lower than in studies of emotion recognition in schizophrenia (180). In addition, the study did not include biological verification that participants were not substance-affected at the time of assessment, or biological measurement of amounts or patterns of drug use. This approach is consistent with that used in other studies of similar populations, and self-report has been found to be a valid and reliable indicator of drug use, particularly when there is no perceived gain or benefit associated with under-reporting of drug use (181, 182). Instruments such as the Timeline Followback method used in our study utilize a structured approach, with anchors and prompts to improve recall and minimize retrospective bias, and a high sensitivity and specificity for past- month substance use (183). Nevertheless, we cannot completely exclude the possible impact of substance use and intoxication on cognitive performance in this study. Finally, while we controlled for general cognitive ability using a measure of IQ, we did not have a measure of pre-morbid intelligence which may have provided a better assessment of this potential confound.

In conclusion, we found impairment in FER was associated with positive psychotic symptoms in individuals who used methamphetamine regularly, despite adjustment for levels of methamphetamine use. We also found preliminary evidence that heterogenous symptom profiles in MAP may also correlate with variation in cognitive correlates. The discrete deficits in emotion recognition identified in people with suspiciousness in our sample are similar to that observed in schizophrenia cohorts. Given the consistent association of FER and social cognition with positive psychotic symptoms in primary psychotic disorder, this novel finding of a similar association in subthreshold MAP has implications for our understanding of substance-induced psychotic disorders within the continuum of psychosis experiences. The identified association between FER and psychotic symptoms in this study supports the concept that MAP shares the same underpinning neurobiological process as psychotic symptoms in primary psychotic disorders. These findings have nosological implications for how MAP and other substance-induced psychotic disorders are conceptualized, and lead to a range of directions for future research to clarify how MAP is understood and treated.

Chapter 8

Facial emotion recognition in MAP compared to healthy controls

8.1 PREAMBLE

In Chapter 7, we found evidence of an association between facial emotion recognition and psychotic symptoms in methamphetamine-using adults. A critique of previous studies of cognition in substance use cohorts has been a lack of comparison of results to healthy control participants. In addition, we previously examined psychotic symptoms as a continuous outcome measure without setting a threshold for clinical level of symptom severity. This allowed us to conduct initial exploratory analyses with a larger overall sample size. Here, we investigated differences in emotion recognition between methamphetamine users with and without *clinically significant* past month psychotic symptoms, compared to healthy control participants. This manuscript was submitted for publication as a brief report in the Journal of the American Medical Association (JAMA) in August 2018 and was rejected. It is currently under preparation for resubmission to an alternative journal.

Declaration for Thesis Chapter 8

Monash University

Declaration by candidate

The following manuscript was submitted for publication in August 2018 and was rejected in August 2018. It is currently in preparation for resubmission.

In the case of Chapter 8, the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Conceptualisation, data collection, data analysis, manuscript preparation	70%

The following co-authors contributed to the work. If co-authors are students at Monash University, the extent of their contribution in percentage terms must be stated:

Name	Nature of contribution
A/Prof Rebecca McKetin	Review of manuscript
A/Prof Antonio Verdejo-Garcia	Review of manuscript
Dr Adam Rubenis (10%)	Data collection
Ms Rebecca Fitzpatrick (10%)	Data collection
Prof Dan Lubman	Supervision and review of manuscript

The undersigned hereby certify that the above declaration correctly reflects the nature and extent of the candidate's and co-authors' contributions to this work*.

Candidate's Signature	[redacted]	**Date** 02/09/18
Main Supervisor's Signature	[redacted]	**Date** 02/09/18

*Note: Where the responsible author is not the candidate's main supervisor, the main supervisor should consult with the responsible author to agree on the respective contributions of the authors.

Title: Methamphetamine use, psychotic symptoms and emotion recognition

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Manuscript word count: 1329 words

Key points

Question: Are psychotic symptoms in methamphetamine-using adults associated with problems in recognising specific emotions in others?

Findings: In this cross-sectional study of 103 methamphetamine-using adults compared to 48 healthy control participants, we found psychotic symptoms in methamphetamine users were associated with significantly poorer recognition of facial emotions, especially anger.

Meaning: Methamphetamine-using adults with psychotic symptoms present with problems recognizing facial emotions in others.

Abstract

Importance: Psychiatric emergencies involving methamphetamine intoxication are often complicated by severe agitation and violence risk, which can necessitate high-risk and resource-intensive sedation and restraint procedures. Methamphetamine use is associated with a dose-related increase in the risk of violent behaviour and this risk is further increased by concurrent psychotic symptoms. Currently there is limited understanding of the underpinnings of violence risk in this situation to guide de-escalation and management. Deficits in facial emotional recognition (FER) have been shown to moderate aggression risk in primary psychotic disorders. However, the relationship between FER and methamphetamine-related psychotic symptoms has not been investigated.

Objective: We hypothesized that methamphetamine users with psychotic symptoms would have poorer FER compared to methamphetamine users without psychotic symptoms, and healthy controls.

Design: Cross-sectional study

Setting: Participants were recruited from treatment and community settings

Participants: Methamphetamine-using participants with (n = 30) and without psychotic symptoms (n = 73) and healthy controls (n=48).

Main Outcome(s) and Measures: We assessed FER in relation to past month positive psychotic symptoms. FER in the past month was assessed using the Ekman Faces Test. Clinically significant positive psychotic symptoms were defined as a score of 4 or more on the Brief Psychiatric Rating Scale.

Results: Methamphetamine users with psychotic symptoms had significantly poorer FER (adjusted OR 0.77 (95% CI 0.60- 0.99)), particularly recognition of anger (OR=0.57(95% CI 0.36- 0.92)), relative to healthy controls. Methamphetamine users without psychotic symptoms did not have significantly different overall FER or recognition of any discrete emotions compared to healthy controls.

Conclusions and Relevance: Methamphetamine users with psychotic symptoms have specific deficits in recognition of anger that could underpin interpersonal aggression risk, and may necessitate optimized de-escalation strategies in acute health settings.

1. Introduction

Up to 50% of individuals with methamphetamine dependence are estimated to have a history of aggression and violence[1], resulting in a substantial burden on acute health services[2]. Psychotic symptoms are common in people who use methamphetamine (MA) regularly and are recognized to contribute to a risk of violence in this population [3]. While impairments in social cognition and facial emotion recognition (FER) have been considered as a potential link between aggression and psychotic symptoms in people with schizophrenia [4], this has not been previously investigated in substance-induced psychotic disorders. It has been proposed that difficulties in recognizing the emotions of others can contribute to hostility by increasing the perception of the environment and cues as threatening [4]. While there is some evidence supporting impaired FER in methamphetamine dependent populations, previous studies have failed to measure and account for the influence of psychotic symptoms, or to consider the degree of these impairments with reference to healthy participants [5]. Here, we sought to investigate specific impairments in recognition of discrete emotions in individuals using methamphetamine, and to understand the relevance of these impairments in relation to healthy controls. We hypothesized that methamphetamine users with psychotic symptoms would have poorer FER compared to methamphetamine users without psychotic symptoms, and healthy controls.

2. Methods

2.1 Participants and Setting

Methamphetamine-using participants were recruited from both public and private residential alcohol and other drug treatment facilities and the community in metropolitan Melbourne, Australia between

March 2015 and February 2017 (n=103), divided into those with past month psychotic symptoms (MAP, n=30) and without psychotic symptoms (MNP, n=73).

Inclusion criteria were (i) being aged 18 or over, (ii) at least weekly methamphetamine use in the past month, (iii) not being currently dependent on drugs other than methamphetamine, nicotine, alcohol or

cannabis, (iv) no previous diagnoses of schizophrenia or bipolar disorder (screened using the Structured Clinical Interview for DSM-IV TR (REF), and (v) no history of loss of consciousness for more than 30 minutes, HIV, epilepsy or any central neurological illness.

Age and gender matched healthy control participants (HC, n=48) were recruited from the same area.

Participants completed informed consent and were reimbursed AU$30. Ethics approval was obtained from the Monash University Human Research Ethics Committee (CF15/40- 2015000222).

2.2 Measures

2.2.1 Psychotic symptoms

Clinically significant past month psychotic symptoms were defined as a score of 4 or greater on any of the Brief Psychiatric Rating Scale (BPRS) [6] positive psychotic symptom items of suspiciousness, hallucinations or unusual thought content.

2.2.2 Methamphetamine use

Days of methamphetamine use in the past month was assessed using the Timeline Followback [7]. Severity of dependence on methamphetamine was assessed with the Severity of Dependence Scale (SDS), with scores ranging from 0 (low) to 15 (high) [8]. Age of first methamphetamine use was based on self-report.

2.2.3 Facial emotion recognition

The Ekman Faces Test (EFT) was used to assess FER [9]. The EFT is a computerized test that presents 60 faces portraying six basic emotions (fear, anger, sadness, disgust, happiness and surprise). Dependent variables were the number of correct identifications for each emotion (ranging from 0-10) and total number of correct identifications (ranging from 0-60).

2.3 Statistical analyses

Firstly, we identified potential confounding sociodemographic and drug use variables that were significantly different between groups using chi-squares and one-way ANOVAs (MAP, MNP, HC groups); and chi-squares and t-tests (MAP, MNP groups).

Secondly, we used a generalised linear model (GLM) to estimate the association between an individual's group membership (MAP, MNP, HC) and their odds of correctly identifying discrete emotions, with HC as the reference group. The model was based on a binomial distribution and a logit link function. The number of trials in the model was 10, that is, the number of faces shown to each individual for each emotion, and the outcome variable was the number of correct identifications. We used a sandwich (robust) estimator for the standard errors in the model, to correct for any potential lack of independence between the 10 attempts for an individual. Both unadjusted and adjusted models are presented, with adjustment for confounds identified in this study (employment) and adjusted for in previous studies of methamphetamine dependence and cognition [5] (age, years of education). All tests were two-tailed with statistical significance set at $p < 0.05$. Statistical analyses were performed using Stata 15 (Statacorp LP, College Station, TX, USA).

3. Results

3.1 Characteristics of sample

Significant differences were found between the three groups for employment status (χ^2=11.20, p=0.004), but not for education or IQ (Table 1). There were no significant differences in methamphetamine use parameters, or other drug use, between the MNP and MAP groups.

(INSERT TABLE 1 AROUND HERE)

3.2 Facial emotion recognition

In comparison to healthy controls (HC), the MAP group performed more poorly on overall emotion

recognition (adjusted OR 0.77 p=0.042), and in recognition of anger (OR 0.54, p=0.010) and sadness (OR 0.58, p=0.012); only recognition of anger remained significantly impaired (OR=0.57, p=0.022) after adjustment.

The MNP group was not impaired in overall emotion recognition (OR 0.94, p=0.618) or recognition of any discrete emotions compared to the HC group.

(INSERT TABLE 2 AROUND HERE)

4. Discussion

Methamphetamine-using adults with past-month psychotic symptoms have poorer overall facial emotion recognition, particularly for expressions of anger, compared to those who used and did not have psychotic symptoms, and healthy controls. This may possibly be a mediating factor in aggression seen in acute psychiatric emergencies involving methamphetamine-related psychosis.

A recent meta-analysis identified social cognition and facial emotion recognition as one of the key cognitive domains most likely to be impaired in methamphetamine dependent individuals, but no studies to date have accounted for the effect of psychotic symptoms on social cognitive performance[5]. In fact, we found that methamphetamine-using participants without psychotic symptoms performed similarly to healthy controls, suggesting that recent psychotic symptoms may be a key driver of impairment in social cognition in this population.

The specific finding of impaired recognition of anger has implications for understanding how people with methamphetamine-associated psychosis interact with others. For instance, this could serve as a mechanism underpinning aggressive behaviour in methamphetamine-using populations. Positive psychotic symptoms have an established association with violence [10] and if this is associated with poorer emotion recognition in methamphetamine users, this could lead to misinterpretation of threat, resulting in individuals responding pre-emptively in an aggressive manner to benign social stimuli [11].

Importantly, there is a dearth of evidence to guide de-escalation for aggression in psychosis, with a recent Cochrane review failing to identify any trials in this area [12]. Poorer recognition of anger in acute methamphetamine psychosis has important clinical implications for treatment providers in emergency

and acute health settings, where particular attention may need to be paid to non-verbal and facial communication skills to support more effective de-escalation.

The cross-sectional nature of our study prevents any inference about the direction or nature of the relationship between methamphetamine use, psychotic symptoms and impairment in emotion recognition. However, we used a structured diagnostic interview (SCID I/P) to exclude individuals with a history of schizophrenia or bipolar disorder, ensuring that these factors were not responsible for the relationship between psychotic symptoms and impaired recognition of facial emotions. We also statistically adjusted for age, employment and years of education in our multivariate analysis. Although we had a fairly small sample size for positive psychotic symptoms (n = 30), this was comparable to previous studies of cognition in methamphetamine psychosis [13,14].

In conclusion, our study provides preliminary evidence of emotion recognition deficits in methamphetamine users who experience psychotic symptoms. Future research in this area could provide novel avenues for intervention and treatment.

Funding body agreements and policies

Author SA is supported by an Australian National Health and Medical Research Council (NHMRC) Postgraduate Scholarship (GNT #1093778), the Windermere Foundation 2016 Syd Allen Fellowship, and a Royal Australian and New Zealand College of Psychiatrists (RANZCP) Research and Education Foundation Grant.

Acknowledgements

We would like to acknowledge the study participants, and staff at recruitment sites, for their generosity in contributing to this study.

Table 1
Participant characteristics

	HC* (n= 48)	Methamphetamine-using participants		Test statistic	p- value
		MNP* (n=73)	MAP* (n= 30)		
Male, n (%)	37 (77)	51 (70)	26 (87)	χ^2= 3.34	0.189
Age (mean, SD)	31.1 (8.67)	32.9 (8.96)	31.7 (7.50)	F=0.65	0.524
Unemployed, n (%)	23 (48)	53 (73)	23 (77)	χ^2=11.20	0.004
Years of education (mean, SD)	13.3 (2.07)	13.2 (2.86)	12.3 (2.15)	F=1.61	0.203
IQ (mean, SD)	101.1 (13.39)	96.8 (11.45)	96.5 (11.9)	F=1.87	0.158
Methamphetamine and other drug use					
Frequency of use (mean, SD)	-	21.4 (10.00)	23.7 (8.46)	t=-1.09	0.277
Age of Onset (mean, SD)	-	24.3 (8.39)	23.2 (8.37)	t=0.03	0.973
Severity of Dependence (SDS) (mean, SD)	-	10.0 (3.65)	11.3 (3.56)	t=-1.66	0.100
Cannabis Dependence, n (%)	-	15 (20.55)	9 (30)	χ^2=0.92	0.338
Alcohol Dependence, n (%)	-	5 (6.84)	2 (6.67)	χ^2=0.00	0.947

*HC: Healthy Controls MNP: Methamphetamine use, no psychotic symptoms MAP: Methamphetamine use, psychotic symptoms

Table 2 Discrete emotion recognition and psychotic symptoms

	HC (n=48)		MNP (n=73)		MAP (n=30)			Unadjusted OR (95% CI)	p-value	Adjusted OR (95% CI)*	p-value
	M	SD	M	SD	M	SD					
Total emotion recognition score	46.58	5.89	45.93	7.45	42.80	4.78	HC MNP MAP	0.94 (0.74-1.20) 0.72 (0.57-0.91)	0.618 0.004	0.94 (0.73- 1.19) 0.77 (0.60- 0.99)	0.593 0.042
Anger	7.78	1.88	7.16	1.77	6.53	2.03	HC MNP MAP	0.72 (0.48- 1.08) 0.54 (0.34- 0.86)	0.115 0.010	0.69 (0.46-1.05) 0.57 (0.36- 0.92)	0.084 0.022
Disgust	7.02	2.14	7.11	2.20	6.50	1.61	HC MNP MAP	1.04 (0.69-1.57) 0.79 (0.52- 1.19)	0.851 0.255		
Fear	6.50	2.30	6.48	2.22	5.93	2.49	HC MNP MAP	0.99 (0.68-1.47) 0.79 (0.48-1.28)	0.964 0.334		
Happiness	9.78	0.59	9.55	0.99	9.53	0.78	HC MNP MAP	0.48 (0.17-1.33) 0.46 (0.15-1.36)	0.160 0.161		
Sadness	7.17	2.02	7.08	2.35	5.97	1.85	HC MNP MAP	0.96 (0.63-1.45) 0.58 (0.38-0.89)	0.845 0.012	1.00 (0.66-1.51) 0.67 (0.43-1.05)	0.991 0.082
Surprise	8.33	1.57	8.52	1.61	8.33	1.30	HC MNP MAP	1.15 (0.72-1.84) 1.00 (0.61-1.63)	0.553 1.000		

*adjusted for age, employment and years of education

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8.2 SUMMARY

This study demonstrated that methamphetamine-using individuals with psychotic symptoms present with impairments in the facial recognition of emotions, and specifically in recognizing anger, compared to healthy controls, and people who use methamphetamine but do not have psychotic symptoms. In the next study, we conducted further analyses to understand whether emotion recognition impairments differed based on the symptom subtype of MAP.

Chapter 9

Discussion and Conclusions

The broad aims of this thesis were to develop a better understanding of the correlates and risk factors for MAP, from sociodemographic and clinical correlates, to novel cognitive markers.

The thesis took a multi-method approach to achieving these aims. Firstly, I undertook an analysis of an ambulance attendance dataset to identify whether there were any demographic correlates that distinguished acute MAP from primary psychotic disorder in this pre-hospital cohort (Chapter 4). Secondly, I performed a clinical audit of a sample of treatment-seeking methamphetamine-dependent individuals to examine clinical correlates of MAP in an outpatient setting (Chapter 5). Subsequently, a systematic review was undertaken to consolidate contemporary evidence on the risk factors and correlates of MAP (Chapter 5). Finally, we recruited a cohort of adults with frequent methamphetamine use for Chapter 7-8, in whom we investigated cognitive correlates of MAP and explored potential associations between these markers and symptom subtypes in comparison to healthy control participants.

The aims and design of the studies in this thesis are summarized briefly below and will be followed by a discussion of their key findings, limitations and strengths, and a general discussion of the contributions of this thesis to the literature.

10.1. CHAPTER 4: SOCIODEMOGRAPHIC CORRELATES OF MAP IN ACUTE AMBULANCE SETTINGS

The aim of the study in Chapter 4 was to investigate the demographic correlates of MAP in a pre-hospital sample. Prior to this thesis, there was little evidence to support differences between acute presentations of MAP and primary psychotic disorder. Several authors had argued that it was extremely difficult, if not impossible, to distinguish between MAP and primary psychotic disorders (such as schizophrenia) based on acute symptoms alone, in terms of the nature and severity of positive psychotic symptoms or the prevalence of negative symptoms (23, 184). However, MAP and primary psychotic disorders related to different aetiological formulations, treatment targets and clinical pathways, and long-term prognoses (23). Consequently, there was a need to explore other variables that could assist in differentiating between acute presentations of MAP and non-drug related psychosis in order to assist clinicians faced with this diagnostic dilemma. Demographic correlates had not previously been investigated in comparison to primary psychotic illness in pre-hospital settings, so we sought to examine this in a large dataset of acute ambulance presentations ("The Ambo Project")(185).

We analyzed this dataset of all ambulance attendances in Victoria, Australia for the period January 2012 to August 2014, comparing presentations for MA-related psychosis presentations (n= 627) to presentations for primary (non-drug) psychosis (n=8184). We found that MA was the drug most commonly implicated in substance-induced psychosis presentations to ambulance services in Victoria. In comparison with primary psychosis presentations, a significantly higher proportion of MA-related psychosis presentations involved younger men, with no previous history of psychosis. MA-related presentations were significantly less likely to involve self-harm, and more likely to require police co-attendance. Further, MA-related psychosis presentations had a similar impact and burden on ambulance services compared to primary psychosis presentations, in terms of the amount of time taken, and the proportion of people requiring transport to hospital. In summary, these findings identified demographic and presentation-related characteristics that differed between the two types of acute presentation. The results are also consistent with the growing literature supporting the burden of methamphetamine use on acute health services, with a study by McKetin and colleagues estimating that between 28 400 and 80 900 additional psychiatric hospital admissions and 29 700 and 151 800 additional emergency department presentations in 2013 in Australia were attributable to methamphetamine use (7). As discussed by McKetin et al, a significant

proportion of these acute presentations involve psychotic symptoms and are resource-intensive and costly to manage.

A key strength of this study was the ability to analyze data from the "Ambo Project" (185, 186), a unique world-first dataset that enables comparisons and trends at a population health level. An important advantage of the dataset is the size and breadth of the database, providing a highly representative picture of acute mental health harms related to alcohol and other drug use. Further, the rigorous methodology employed to extract and code information in the "Ambo Project" ensures robustness of the data (185, 187).

However, characterization of clinical information at an individual level is difficult with this type of data. Presentations were coded as psychosis if the paramedics at the scene identified psychotic symptoms as being the primary reason for the attendance. Importantly, this does not equate to a diagnosis of methamphetamine-induced psychotic disorder; rather, the presentations in this dataset are also likely to include symptoms of psychosis that arise in intoxication or withdrawal syndromes. In addition, the accuracy of the data depends on the clinical assessment and information available to the paramedic at the scene, and if substance use is not identified and documented by the paramedic, the presentation may be missed. Similarly, the data only reflects presentations where an ambulance was called and therefore may not be reflective of cases of psychosis in the community more broadly. As such, the data in this study is likely an underrepresentation of drug-induced psychotic presentations. In addition, clinical information, such as psychiatric diagnoses, psychiatric history and drug use patterns, may not be routinely collected by the paramedic as such information may not be considered salient to the emergency presentation. Consequently, this method may not be appropriate for the assessment of individual-level clinical data that may be pertinent to risk of MAP.

10.2. CHAPTER 5: CLINICAL CORRELATES OF MAP IN A STIMULANT-SPECIFIC TREATMENT SETTING

Therefore, in Chapter 5, we aimed to examine the correlates of MAP within a stimulant-specific alcohol and other drug (AOD) treatment service. The rationale for this study was informed by the evidence supporting methamphetamine-related factors (such as frequency of use) as the main risk factor for MAP (42). However, previous studies had largely been based on cohorts of treatment-seeking individuals in 'mainstream' AOD services. There is a widely-acknowledged treatment gap for methamphetamine use disorders (188), and methamphetamine-using individuals within treatment settings often present late in their trajectory of use with more

severe disorders. Severe addictions are often associated with a range of other psychosocial complexities, such as homelessness or financial stress, and these factors are difficult to separate from the drug use itself, potentially confounding the relationship between methamphetamine use and MAP. As such, there was a gap in the evidence relating to people with less severe methamphetamine-use disorders or higher function, and it remained unclear whether methamphetamine use patterns would still be the primary risk factor for MAP in such cohorts.

In order to study this, we undertook a clinical audit of the records of clients attending a specialized stimulant treatment service in Melbourne (n= 175) between 2008 and 2014. Information was collected on sociodemographic, clinical and drug use variables. For the outcome of MAP, we compared individuals with a self-reported lifetime experience of psychotic symptoms whilst using methamphetamine, to those without a history of psychotic symptoms.

We found a 48% lifetime prevalence of self-reported psychotic symptoms in this study. Further, we found that the frequency of methamphetamine use was significantly associated with the likelihood of a lifetime experience of psychotic symptoms. Almost half the sample (44%) reported using methamphetamine weekly or less than weekly, and 53% reported duration of use of less than five years. Our findings were consistent with previous literature that supported methamphetamine frequency as being the most consistent risk factor for MAP (42), despite the sample being relatively high-functioning compared to other Australian samples on sociodemographic and drug use indices.

Data in this study was collected as part of routine clinical care with expected limitations, such as gaps arising from missing data. Other limitations included the lack of standardized outcome measurement, and the reliance on retrospective self-report. The sample attending this specialist stimulant clinic may not be representative of treatment-seeking methamphetamine-use populations elsewhere; indeed, we highlighted the differences between this cohort and others in Australia, demonstrating that this group were higher-functioning and presenting earlier in their use trajectory. This affects the generalizability of our findings. In addition, within this cross-sectional audit, we were unable to ascertain if psychotic symptoms reported by participants were pre-existing, whether they arose in the context of methamphetamine intoxication or withdrawal, or if they persisted during periods of sobriety. However, this methodology was similar to that used in a number of previous studies in the area (51), and the

results provided an original contribution to the literature by focusing on an 'early-intervention' cohort reached through a specialist stimulant-specific clinic.

10.3. CHAPTER 6: SYSTEMATIC REVIEW ON RISK FACTORS AND CORRELATES OF MAP

The aim of the study in Chapter 6 was to consolidate and synthesize the existing literature on correlates and risk factors for MAP, by means of a systematic review. While individual studies had reported on a range of correlates of MAP, there remained a lack of consensus on what factors were the most salient and consistent predictors of the disorder (22). In addition, there were significant differences in the way psychosis was defined and measured in individual studies, so it was difficult to develop an understanding of what the literature showed. Consequently, we undertook a review of correlates of MAP utilizing systematic review methodology.

Briefly, the systematic review methodology involved a search for studies reporting on associations between psychotic symptoms (or disorders) and illicit methamphetamine use in adults. We excluded case reports, literature reviews or studies in animals. We aimed to categorize risk factors/correlates according to the following domains developed *a priori*, including (i) sociodemographic (age, gender, employment, education, housing), (ii)drug-related factors (methamphetamine use amount, frequency, duration of use, age of onset of use, route of use), and (iii) non-drug related factors (family history of psychotic or other psychiatric illness, history of trauma).The search was conducted across three databases (Medline (OVID), PsycINFO and EMBASE), as well as manual searching of the reference lists of previous reviews, and citation searching using Google Scholar. The review protocol was developed in accordance with the PRISMA guidelines and was registered *a priori* on PROSPERO (International Prospective Register of Systematic Reviews).

We included 20 studies across 13 separate populations, with a total of 5476 participants. We found that drug-related factors (methamphetamine use frequency, severity of dependence) were the most consistent correlates of psychotic symptoms in people using methamphetamine. Our systematic review did not identify strong evidence for non-drug risk factors for MAP, such as a family history of psychotic illness or a history of trauma. This was in part due to the paucity of studies in this area; for example, only one study examined childhood trauma as a risk factor. Importantly, only five studies in the review assessed current psychotic symptoms in relation to

contemporaneous measurement of methamphetamine use. The majority of studies investigated lifetime experiences of psychotic symptoms against current drug use measures.

The limitations of this study apply to systematic reviews in general, in that the limitations of the studies included affect the overall strengths and weaknesses of the review. Firstly, we were only able to identify 20 studies in total (on 13 different populations). There was significant variability in outcome definition and assessment, and in reporting of measures of association, meaning that we could not undertake a quantitative synthesis or meta-analysis due to both qualitative and statistical heterogeneity. Similarly, we assessed the overall quality of the evidence as low-moderate (with reference to the GRADE criteria (189). The risk of bias was highly variable, and the most common reasons for lower quality ratings (with reference to a modified version of the Newcastle Ottawa scale (190) was due to the lack of exclusion of a pre-existing psychotic disorder. This is an important limitation as almost all of the included studies were cross-sectional in design.

Nevertheless, this study was the first comprehensive and systematic review to examine correlates of psychosis amongst people who use illicit MA. Strengths of the review included a systematic review protocol registered *a priori*; and searches, data extraction and quality assessment performed independently by two co-authors. The review provided an original contribution to the literature on MAP, given that previous searches had not been of a systematic nature, and had not included a qualitative or narrative synthesis of the evidence (22, 23, 145). In addition, the results of this review contributed to understanding the key correlates of psychotic symptoms that would need to be assessed and adjusted for the subsequent studies in the thesis. The review was conducted whilst awaiting ethics approval for these studies and provided an opportunity to develop a skillset in systematic review approaches, as well as a means to produce a comprehensive and rigorous overview of the evidence.

The key message from this study was that treatment of methamphetamine use was itself an essential and central part of treatment (and prevention) of MAP. Given that methamphetamine use (use frequency, severity of dependence) represents a modifiable and treatable risk factor in the development of psychotic symptoms, our results highlighted the importance of targeting this as a potential means of early intervention in MAP.

Chapters 7-8 of the thesis involved primary data collection through recruitment of a cohort of methamphetamine-using adults, and a group of healthy control participants, focusing on investigating cognition as a potential marker of MAP.

10.4. CHAPTER 7: WHAT ARE THE COGNITIVE AND SOCIAL COGNITIVE CORRELATES OF MAP?

The aim of the study in Chapter 7 was to examine cognition and social cognition in a cohort of methamphetamine-using adults. We hypothesized that positive psychotic symptoms would be associated with impairments in cognition (verbal memory and recall, impulsivity in decision-making) and social cognition (facial emotion recognition) in people who used methamphetamine regularly (n=103). In this study, age, gender and other drug use (alcohol or cannabis dependence) were not found to be associated with any of the predictor variables and so were not adjusted for as potential confounders. We therefore investigated associations between past month positive psychotic symptoms and cognitive variables, adjusting for methamphetamine use (severity of methamphetamine dependence), and IQ.

We did not find any evidence of an association between cognitive domains and psychotic symptoms. However, we found that facial emotion recognition was impaired in people with methamphetamine use with positive psychotic symptoms, even after accounting for methamphetamine use severity and other potential confounders. To our knowledge, this is the first study to identify an association between MAP and FER impairment. These novel findings provide an original contribution to the literature on MAP, supporting potential commonality between MAP and primary psychotic disorder.

As discussed in the introduction (Chapter 1), the literature review (Chapter 2) and systematic review (Chapter 6), MAP was shown to be a heterogeneous disorder with variations in presenting symptom profiles in different studies. Previous authors have highlighted the need to precisely characterize predominant symptoms and phenomenology (90, 191), as this may have implications for prognosis and trajectory (85). As such, in this study we also aimed to investigate whether different positive psychotic symptoms were associated with differences in patterns of recognition of discrete emotions (FER). We undertook sub-analyses of FER performance, with the total Brief Psychiatric Rating Scale score for each positive psychotic symptom item (suspiciousness, hallucinations, unusual thought content) as the primary outcome.

Overall, we found limited evidence that specific subtypes of psychotic symptoms in MAP correlate to impairments in recognition of discrete emotions. Following adjustment for

potential confounders (age, gender, years of education, severity of methamphetamine dependence), there was only a significant association between past month suspiciousness and poorer identification of disgust. This finding could potentially relate to a true association between this symptom subtype and difficulties in recognition of disgust, with previous studies finding an association between deficits in disgust recognition and dopamine dysfunction in the basal ganglia in Parkinson's Disease (172). However, few participants in our study had severe psychotic symptoms, and this was particularly true for the 'unusual thought content' item on the BRPS, with only 4 participants scoring more than 4 on this scale. Consequently, this result cannot be translated to clinical or hospitalized populations with more severe psychotic symptoms or a diagnosis of methamphetamine-induced psychotic disorder.

The sample in this study had a fairly homogenous pattern of methamphetamine use compared to populations in previous studies. The majority of the sample (58.2%) reported daily or almost daily use of methamphetamine in the month prior to assessment. Not only was average frequency of methamphetamine use high, but this sample also had a low variance in frequency of methamphetamine use (see Figure 1 below). This homogeneity in methamphetamine use frequency may account for the failure of this study to replicate an association between methamphetamine use frequency and likelihood of psychosis symptoms, as found by several other authors (42, 47, 101). For instance, in comparison, the MATES cohort recruited by McKetin and colleagues only had a third of the sample reporting frequency of use of more than 16 days in a month (42). In contrast, while the mean severity of methamphetamine dependence in this cohort was high (Mean SDS= 10.37), there was considerable variation in severity of dependence, with severity of dependence scale (SDS) scores ranging from 0 to 15 (see Figure 4 below). This is likely to have been the reason that severity of methamphetamine dependence was found to have a significant association with positive psychosis symptoms, but methamphetamine use frequency was not.

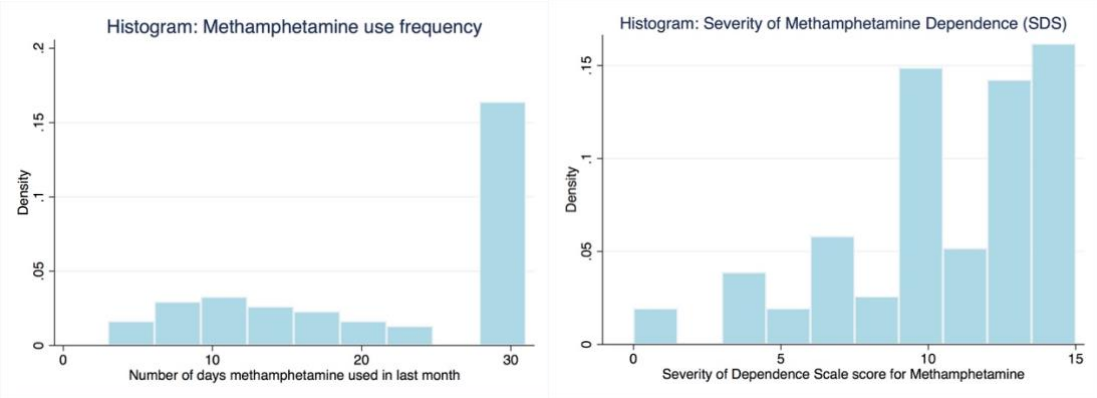

Figure 4: Histograms for methamphetamine use frequency and severity in Study 4

This limitation arose from the sampling strategy, with the substantial majority (80%) of participants being recruited from residential detoxification treatment settings. While this is common practice in many studies of illicit drug use populations, this approach does result in a bias towards participants with more severe substance use disorders and higher frequency of use. This is particularly true for methamphetamine use, where the withdrawal syndrome does not routinely require medication treatment in an inpatient setting, or the monitoring or management of medical risk. Consequently, it is the individuals with daily or almost daily use who are likely to prefer detoxification in a residential treatment setting, whereas people with less frequent use may find community or home-based treatment approaches adequate for their needs. While this was recognised as a limitation of the methodology that was likely to introduce bias, the strategies we utilized to recruit from community/non-treatment seeking settings were largely unsuccessful. Firstly, we attempted to recruit using flyers and placement of research staff at needle syringe programmes (NSPs), similar to the methods used by other studies in Australia (36, 179, 182). However, a major barrier to recruitment from NSPs was the exclusion of participants with opioid use disorders, resulting in ineligibility of most clients attending our NSP recruitment sites. Similarly, the length of the interview schedule and cognitive battery in this study was another challenge to NSP recruitment as previous studies that have successfully recruited through NSPs have had much shorter interviews (e.g. Lapworth et al's study involved a 40 minute interview)(179). The second strategy utilized to boost community recruitment was the use of advertising in street press and music magazines. This has previously been demonstrated to be a highly successful recruitment method in other methamphetamine studies in Melbourne (192) and in other Australian cities (5, 49). While a brief advertising campaign resulted in a small number of participants recruited from the community in our study, this was an essentially unfunded study, and we had limited budget to invest in sustainable and larger-scale advertising strategies. Consequently, the substantial majority of the recruitment for this study was based on recruitment from residential treatment settings.

Given that this was a cross-sectional study, we could not determine the direction of association between psychotic symptoms and FER impairment. We sought to control for some potential confounders with statistical analysis, using a non-parametric regression model that adjusted for age, gender, current IQ, severity of methamphetamine dependence, and alcohol and cannabis dependence. The identification of these confounding factors was based on previous reviews of cognition in substance dependence (127, 193). Nevertheless, there could be other unmeasured confounders that impacted on the relationship of the variables of interest.

The study had a naturalistic approach to sampling with regards to inclusion and exclusion criteria pertaining to use of drugs other than methamphetamine. We aimed to enhance the external validity of the study, with a greater likelihood that the results would translate to real-world settings. As such, the decisions regarding the exclusion and inclusion criteria pertaining to other substance use reflected a compromise between rigor and feasibility, and the aim of minimising the impact of other drugs on the cognitive and social cognitive tasks in this study. In this study, there was no exclusion criteria relating to the current use of alcohol and other drugs, only with regards to use disorder/ dependence diagnoses. Participants who were dependent on nicotine, alcohol and cannabis were able to participate, but this was assessed, diagnosed (using the SCID I/P)(30) and measured in terms of severity of dependence (using the severity of dependence scale (SDS) with validated cut-offs for alcohol and cannabis(164)). Nicotine, alcohol and cannabis use are very common in the Australian population, with even higher prevalence rates reported in people seeking treatment for alcohol and other drug use (4). Although there is literature supporting the impact of nicotine (194), alcohol (195) and cannabis (196) use and dependence impacting on cognitive performance, it was anticipated that excluding participants reporting use of these drugs would both serve as a significant barrier to recruitment, and also impact on the representativeness of the sample. Only a low proportion of participants met criteria for alcohol use disorder (n=7, 6.8%, mean SDS=1.54) and cannabis use disorder (n=24, 23%, mean SDS=2.48).

In addition, our study did not incorporate biological verification of substance intoxication or antecedent substance exposure. Rather, participants were informed of the need to abstain from their substance of choice on the day of the assessment; and recent substance use was based on self-report, using a structured and validated assessment tool, the Timeline Followback Scale (163). Practical challenges to biological verification included cost, feasibility and concern that

this would be a potential barrier to recruitment. Darke and colleagues have previously demonstrated that participants' self-report is a valid reflection of recent substance use (181), with structured approaches to measuring drug use history such as the Timeline Followback further improving validity compared to biological measurement (183). Similarly, Rowe and colleagues recently compared self-reported methamphetamine use over the previous 3 days to urine toxicology, finding a positive predictive value (PPV) of 91.5% (95% CI 86.9- 94.8%), and negative predictive value (NPV) of 78.0% (95% CI 69.4- 86.1%) (197). Even in some studies that have used hair sampling and analysis using GCMS (gas chromatography and mass spectrometry), results of hair testing have generally been demonstrated to be comparable to self-report. For instance, in McKetin and colleagues 2013 study, results of hair toxicology on a subset of participants were concordant with self-report 73% of the time (94% specificity, 60% sensitivity), with only 6% of people who self-reported past month abstinence having a positive hair test (182). In addition, there is still some debate as to the reliability of correlation between the dose and the concentration of drugs tested for in hair analysis (198), and in one study, hair analysis was found to significantly under-detect self-reported MA exposure (199).

Keeping these limitations in mind, this study is one of the largest to date to assess cognition in MA users, and the first to assess FER in relation to psychotic symptoms. The key findings provide original contributions to the literature on MAP and will be discussed in further detail in the sections below.

10.5. Chapter 8: how do cognitive and social correlates of MAP compare to healthy control participants?

A common critique of previous studies of cognition in methamphetamine dependence has been the lack of a healthy control reference group, and the difficulty in estimating the degree of impact cognitive impairment may have on function within the real-world context (127, 131). For instance, Hart has previously pointed out that in many studies of cognition in methamphetamine-using adults, participants perform similarly to controls across many cognitive domains (131). In the few cognitive domains where there is evidence of cognitive impairment (such as sustained attention, impulsivity and verbal memory and learning), studies often do not take into account normative data (age and education-adjusted) for the group, making it difficult to assess whether changes in cognitive performance are clinically meaningful (131).

In the study in Chapter 7 we established an association between FER and psychotic symptoms,

but the degree of FER impairment in relation to a healthy control population remained unclear. In addition, psychotic symptoms in the study in Chapter 5 were assessed as a continuous measure; that is, the total score across the three positive psychotic symptom domains on the Brief Psychiatric Rating Scale (BPRS). However, individuals scoring <4 on the BPRS have mild symptoms that are unlikely to be clinically meaningful. Here, we aimed to assess differences in FER in individuals with clinically significant psychotic symptoms (≥4 on any of the BPRS positive psychotic symptom domains, following the method used by Mcketin et al (49)). We hypothesized that FER performance in people with methamphetamine use and clinically significant past month positive psychotic symptoms (MAP group, n=30) would be poorer compared to people with methamphetamine use and no psychotic symptoms (MNP group, n=73), and healthy control participants (HC group, n=48). We recruited a healthy participant group via advertising from the university campus and surrounding regions, ensuring that controls did not significantly differ from the methamphetamine-using group in gender or age. We compared overall FER performance, and scores for recognition of each of the six basic emotions, across groups after adjusting for potential confounds (age, gender, IQ, severity of methamphetamine dependence and polydrug use (alcohol and cannabis dependence)).

The key finding of this study was that the MAP group had significantly poorer overall FER performance in comparison to both the MNP and HC groups; and the MNP and HC groups had similar performance. On analysis of recognition of specific emotions, we found that anger recognition is particularly impaired in MA users with psychotic symptoms.

Given the study's cross-sectional design, we were unable to ascertain the nature and direction of the association between FER and psychotic symptoms. We also had a limited sample size in our MAP group (n=30). In addition, future research could use a more comprehensive task to assess FER. The emotion recognition task used in our study did not enable us to identify the nature of errors in identification of anger- that is, whether individuals were identifying anger as another specific emotion. Further, our task lacked a neutral face, meaning we could not ascertain if there was any misidentification of neutral faces as anger. Similarly, intensity effects could not be examined in the context of this study.

In summary, the study in Chapter 8 provided first evidence of FER impairment in methamphetamine-using adults with psychotic symptoms compared to those without psychotic symptoms, and healthy controls. This result brings a novel perspective to previous

evidence of impairments in FER in people with methamphetamine dependence (127, 193), suggesting that psychotic symptoms may be the factor associated with FER impairment, rather than methamphetamine use itself. Importantly, while previous studies excluded individuals with a diagnosed psychiatric (or psychotic) *disorder*, they did not exclude participants with recent or current experiences of psychotic *symptoms*. A further outcome from Study 5 was the identification of specific impairments in anger recognition in people with MAP. This has particular clinical salience, given that MAP is often associated with agitation, hostility and aggression. Previous studies in schizophrenia and hostility have suggested that poor recognition of emotions, particularly anger, fear or disgust, can lead to misinterpretation of threat and can moderate violence risk (200). The identification of poorer recognition of anger in this group could inform clinical approaches to management of agitation, and to treatment approaches for MAP and MA dependence.

10.6. General Discussion

Following on from the overview of the individual studies and their main findings, this section comprises an integrated discussion of key contributions of this thesis to the literature, and to examine two specific domains that relate to the research questions in this thesis, laying the groundwork for future research directions. Firstly, the studies in Chapters 4-6 in this thesis sought to investigate evidence for correlates and risk factors for MAP. The outcomes of these studies will be compared and contrasted with the existing literature, focusing on the relationship between MA use and MAP. Secondly, studies in Chapter 7-8 investigated cognitive correlates of MAP and the discussion of these studies will focus on the relationship between FER and MAP.

10.6.1. Correlates and risk factors for MAP: Is It Just About the MA use?

Prior to this thesis, MAP was considered in a similar manner to other substance-induced psychotic disorders within a traditional diathesis-stress model. Following this model, substance use was considered a stress that would trigger psychotic symptoms in individuals with a predisposition or vulnerability to psychosis (22). There was emerging evidence, however, that methamphetamine use was a potent driver of psychotic symptoms, and one study demonstrated that a dose-response relationship existed between MA use and the likelihood of psychotic symptoms (42). The key gaps in the literature related to whether sociodemographic correlates, or other clinical risk factors (for instance, psychiatric history, history of trauma) played a role in MAP, and this was investigated in the studies in Chapters 4-6.

The study in Chapter 4 demonstrated that few demographic variables distinguished between acute presentations of MAP and primary psychotic disorder. Clinical factors were investigated in Chapter 5, and we found that individuals reporting a higher frequency of methamphetamine use (on entry into AOD treatment) had a higher likelihood of a lifetime experience of psychotic symptoms. This finding was consistent with previous literature. In our systematic review (Chapter 6) we again found that drug use factors were the most likely correlates of psychotic symptoms in methamphetamine use populations, and this was also consistent with the results of the clinical audit (Chapter 5). However, methamphetamine use frequency was not associated with psychotic symptoms in Chapter 7. The main reason for this was that the methamphetamine use patterns of the sample in this study differed from populations in previous studies, in terms of the frequency of methamphetamine use and the severity of dependence.

The review in Chapter 6 found little evidence for non-drug correlates of MAP, with only one previous study assessing childhood trauma (40). In terms of family history of psychotic illness, one study found this to be associated with psychotic symptoms in methamphetamine users (201), but three other studies did not (36, 50, 103). While methamphetamine users with persistent psychotic symptoms were more likely to have a family history of psychotic illness in one study, this was not the case for people with brief or transient symptoms (143).

Taken together, the results of the studies in Chapter 4-6 highlight the central role of methamphetamine use as a key modifiable risk factor for MAP, and the relative paucity of evidence for non-drug correlates of MAP. This is unsurprising, given that research conducted as early as the 1960s by Bell and others pointed to the propensity for amphetamine to trigger psychotic symptoms in experimental models (1, 202). The symptoms and behaviour observed in humans in laboratory-based amphetamine administration resembled paranoid schizophrenia, and these symptoms were responsive to phenothiazine antipsychotics (82). Human and animal amphetamine models of psychosis were therefore based on the hypothesis that dopamine neurotransmitter dysfunction subserved psychotic symptoms in schizophrenia (203, 204). Indeed, chronic use of high dose methamphetamine results in neuroadaptation in the dopamine circuitry, with both downregulation of dopamine release and a decrease in dopamine transporter availability observed even up to 9 months abstinence (15). The authors discuss how processes of tolerance and neuroadaptation, rather than neurotoxicity and apoptotic damage, are likely to account for changes in dopamine transmission in vivo (15). These changes, however, reflected adaptation observed across all individuals using methamphetamine; and the meta-analysis did not include sub-analysis of individuals with current or previous psychotic symptoms. As such, it

is unclear whether dopamine dysfunction alone is adequate explanation for high-dose methamphetamine-related vulnerability to psychotic symptoms.

Further, as highlighted in McKetin's recent discussion of experimental studies of amphetamine models of psychosis (27), while there is clear evidence from early work that high-dose use can trigger psychotic symptoms in intoxication, it remains less clear whether this is necessary or sufficient to promote persistent clinical syndromes that resemble schizophrenia. This remains an important question that is difficult to answer, and this debate mirrors the questions raised about the role of other drugs, such as cannabis, in the development of schizophrenia and other primary psychotic disorders (205, 206). Decades of research into the role of cannabis in the pathway towards development of schizophrenia points to a need to better understand how cannabis use interacts with both genetic and other environmental influences, with a growing recognition of the importance of non-drug exposures such as trauma or urbanicity in contributing towards persistent psychotic illness (205). Future research in MAP can draw from the learnings from this literature towards identification of common markers of psychosis-proneness.

In summary, the findings of this thesis strengthen the argument for investigating methamphetamine use as a potential modifiable factor in the pathway to persistent psychotic disorder for the estimated one in three individuals who will transition from methamphetamine-induced psychotic illness to schizophrenia (54, 56), but there remains a significant gap in our understanding of the non-drug correlates of MAP. The studies in Chapter 4-6 in this thesis therefore highlight the need for further research into markers of psychosis-proneness in MAP, including cognition.

10.6.2. Cognition, FER and MAP: Lack of association between MAP and Cognitive impairment

In Chapter 7, psychotic symptoms were not associated with any cognitive impairments other than FER. This was an unexpected finding, given that three other previous studies have identified impairments in cognition in people with MA psychosis (137-139). There were a number of potential explanations for this.

Two previous studies that have found evidence of cognitive impairment in relation to methamphetamine psychosis have had relatively small sizes, ranging from 20-30 participants,

compared to our sample size of 103 (138-141). They may have been underpowered, resulting in an overestimation of the effect size and impact of cognitive deficits, with a false positive finding (Type I error). In contrast, Chen et al (2015) had a methamphetamine-using sample size of n=131, but found no evidence of cognitive impairment in participants with no psychotic symptoms and those with only brief psychotic symptoms, in line with our findings. The Chen study identified cognitive impairments only in the group with persistent psychotic symptoms (n=56).

Another explanation for previous findings of cognitive impairment in other studies of MAP may relate to the effects of anti-psychotic medication. There is some evidence that anti-psychotic medication, particularly first-generation medications with prominent dopamine (D2) antagonist effects, can cause cognitive blunting and reduced performance on neuropsychological tests in healthy volunteers (207, 208). Other authors propose that antipsychotic polypharmacy, sedation and extrapyramidal symptoms (EPS) can cause cognitive impairment (209). Two of the previous studies of MAP and cognition were conducted in individuals who were all prescribed anti-psychotic medication (137, 138). In Chen's study, participants with persistent psychotic symptoms presented with cognitive impairment and had a greater degree of anti-psychotic medication than participants with brief psychotic symptoms who had no cognitive impairment (139). There was no detail provided in their study on whether participants received atypical or typical anti-psychotic medication. However, in their discussion, Chen and colleagues explain that their results indicate the use of anti-psychotic medication was related to poorer performance in executive function in methamphetamine users with persistent psychotic symptoms, but not to performance in other cognitive domains. In contrast, in our study, only 7 (6.8%) participants were prescribed anti-psychotic medication.

Alternatively, the lack of association between cognitive impairment and psychotic symptoms in our study could be that our neuropsychological battery was too narrow and failed to assess domains that were impaired. For instance, previous studies have identified impairments in MAP populations in selective and sustained attention and visual processing (137-139), domains that we did not assess. In addition, we had only one task tapping each domain, so it is possible that our battery was too blunt to detect a true difference, resulting in a Type II error.

Finally, another important possibility is that previous studies that have found cognitive impairment in methamphetamine users with psychotic symptoms have recruited participants with a higher severity of psychosis. Jacobs, Ezzatpanah, Bouchard and Chen's samples have all

been recruited from hospital inpatient, psychiatric outpatient or detention settings, suggesting a higher severity of psychotic symptoms and/or methamphetamine-induced psychotic disorder diagnoses (137, 138, 140). In comparison our study assessed psychotic symptoms of a lower severity in a cohort that was non-treatment seeking for mental health. This may suggest that cognitive impairment may only be present in more severe methamphetamine-related psychotic disorder rather than in cases with sub-threshold symptoms.

The only previous study to assess cognitive function in a group with brief psychotic symptoms (as well as more severe symptoms) was conducted by Chen and colleagues in 2015 (139). They found the cognitive profile in this group to be the same as MA-dependent individuals without psychotic symptoms, and our findings are consistent with their results. Chen and colleagues 2015 study (59) investigated cognition and psychotic symptoms in 106 methamphetamine-using participants versus healthy controls (n=67) and inpatients with schizophrenia (n=54). Their study lends itself to direct comparison with the findings of this thesis, in that they recruited participants with varying duration of psychotic symptoms and included a participant group with brief or transient symptoms- similar to the group within this thesis. The brief psychotic symptom group in the Chen study had no cognitive impairments in comparison to methamphetamine users with no psychotic symptoms; compared with healthy control subjects. The severity of psychotic symptoms in the brief psychosis group in their study was somewhat higher in comparison to our study. Their group had a mean BPRS positive symptom score of 8.8 +/- 1.6, compared to our mean positive score of 5.95 +/- 3.09, but both these scores are substantially lower than what might be considered to meet threshold for clinically significance. The cognitive domains tested by Chen and colleagues included a range of important tasks not investigated in our study (attention and processing speed, for instance), but had consistent results for the domains that did overlap (verbal memory), with no impairment compared to controls. The Chen study did not have any measures of decision-making or impulsivity, so our finding of a lack of impairment in these domains in comparison to controls adds to Chen's results. Taken together, our two studies provide convincing evidence that methamphetamine-using adults (with no psychotic symptoms) or those with low-severity, brief psychotic symptoms do not present with evidence of cognitive impairment.

10.6.3. Significance of the relationship between FER and MAP

The association of FER and MAP has several implications for the understanding of MAP, SIPD and the spectrum of psychosis experiences. This thesis includes a range of studies that, to our

knowledge, were the first to examine FER in any type of substance-induced psychotic disorder. As such, it raises a number of key questions in relation to the nature and direction of the relationship between FER impairment and MAP, and how MAP relates to primary psychotic disorders.

MAP and FER impairment may be associated in a number of ways. Central to this discussion is the consideration of FER impairment as a 'state' or 'trait' phenomenon in MAP.

10.6.3.1. MA-RELATED NEUROADAPTATION LEADS TO IMPAIRMENT IN FER

Firstly, FER impairment may arise as a direct result of MA use. Potvin and colleagues' recent meta-analysis identified social cognition as one of the cognitive domains identified to be most impaired in people with methamphetamine use disorder (Cohen's d= 1.117, 95% CI 0.810-1.423), with more prominent deficits in this domain than in 'traditional' cognitive constructs like working memory or executive function (127). Long-term exposure to MA is known result in potent neuroadaptive effects, impairing dopaminergic neurotransmission in the dorsolateral prefrontal cortex, anterior cingulate cortex, and other striatal regions (15, 129). The neural networks believed to underpin social cognition, and specifically, facial emotion recognition are thought to be in the ventromedial prefrontal cortex and limbic and insular regions (122, 176), but the specific neurotransmitter mechanisms underpinning methamphetamine-related social cognition impairment remain unclear (127). It is possible there may be some overlap between the circuitry believed to be directly damaged in chronic MA use, and that involved in FER. As such, FER impairment seen in populations with chronic MA use may be reflective of direct neurobiological changes resulting from drug use, as suggested by some authors (133, 134), and this may also underpin the process of psychosis. If this is the case, individuals with a greater level of neuroadaptation from higher dose MA use would be assumed to be more likely to present with a greater level of FER impairment. This was not supported by the findings of this thesis, however, as there was no association between MA use frequency or severity and degree of FER impairment (Chapter 7). As discussed in Chapter 7, this failure to detect an association between FER and MA use may be related to a fairly homogenous pattern of MA use in this sample; or it may point to an alternative explanatory model for the association between FER and psychosis.

Similarly, if FER impairment arises from MA use directly, this model would support the idea that cessation of MA use would result in potential resolution of FER impairment, and a reduction in the risk of psychosis. However, in a sample of participants with early abstinence

from MA, there appeared to be lasting FER impairment (133).

10.6.3.2. FER AS A 'STATE' PHENOMENON THAT RELATES TO PSYCHOTIC SYMPTOMS

An alternative explanation is that FER impairment may reflect a neurobiological process relating to psychosis itself. If considered from this perspective, individuals with MAP may present with FER impairment as a result of the underlying neurobiological process of psychosis, regardless of aetiology. This would point to FER impairment as being a result of, rather than a cause of, the psychosis process. Such a model would not fit FER within causative explanations as to why some individuals who use MA develop psychosis, and others do not. Again, given the limitations of our cross-sectional study, our findings cannot answer the unknowns relating to this model as we cannot distinguish between cause and effect. However, in support of this model is evidence that FER impairment has been found to map to psychosis symptoms in a variety of different psychiatric disorders, both those conceived to be 'schizophreniform' in nature, and affective or personality disorders that have psychosis as part of the spectrum of symptoms. In order to answer this critical question, future longitudinal research could prospectively follow methamphetamine-dependent individuals to ascertain whether FER impairment fluctuates with the expression of psychotic symptoms.

10.6.3.3. FER AS A 'TRAIT' PHENOMENON THAT RELATES TO PSYCHOSIS PRONENESS

A third model could be that FER impairment is a pre-existing 'trait' in MAP, and a marker of vulnerability or predisposition to psychosis. This model would posit that impairment in FER would pre-date both the use of MA and psychotic symptoms. This is a theory suggested in the study of schizophrenia and primary psychotic disorders, for instance. It is supported by the discovery of FER impairment in ultra-high risk (UHR) for psychosis cohorts (105, 124, 150, 175, 210). The identification of FER deficits in these cohorts suggests that impairment pre-dates the psychosis process itself. FER impairments have also been found in first-degree relatives of individuals with schizophrenia (150, 211), strengthening the likelihood of the construct as vulnerability marker in schizophreniform psychoses. In terms of MAP, this explanatory model fits well with the traditional diathesis-stress model of schizophrenia and other psychotic disorders, where substance use is considered to a stress or a component cause contributing to psychosis in an individual already predisposed to development of such symptoms (59). This is the model suggested by Bramness and others (22), with MA use triggering psychotic symptoms in already vulnerable individuals. In such a model, FER may be a marker of this underlying vulnerability, potentially mapping to processes that underpin predisposition to MAP or to other

psychotic disorders.

Our findings are also consistent with this model. While we found an overall association between FER impairment and psychotic symptoms (Chapter 7), we also found that individuals with methamphetamine use disorder without psychotic symptoms had no FER impairment in comparison to healthy controls (Chapter 8). As such, our findings support the possibility of FER impairment as a marker of psychosis proneness in MA use populations; but need to be tested by prospective longitudinal research.

10.7. LIMITATIONS AND STRENGTHS

In summary, this thesis utilised a mixed method approach to understand correlates of MAP, with varying limitations and strengths which will be briefly reiterated here.

The study in Chapter 4 was based on analysis of a large, robust and unique population-based dataset but was limited by the lack of individual-level clinical information. In contrast, the audit of clinical records (Chapter 5) enabled greater study of details pertaining to clinical presentation, such as substance use patterns and history, but had a low sample size and involved data that was routinely collected as part of clinical care, with potential inconsistencies and accuracies. Both these studies examined different samples, but both were subject to selection bias, and neither sample is representative of the broader target population of methamphetamine-using adults in the community.

The systematic review (Chapter 6) was the first rigorous attempt to identify correlates of MA psychosis. Previous reviews in this area have not utilised systematic methodology (22, 23). Strengths of the review, as identified in Chapter 6, include prospective registration of the systematic review protocol on PROSPERO prior to data extraction, searches in any language, across multiple databases, with two independent reviewers screening and assessing eligibility of studies and performing data extraction. A further strength of the review was the assessment of methodological quality of existing studies by two reviewers, which had not been previously performed in any other reviews in this area (22, 23, 145). The heterogeneity in study design presented some challenge to quality assessment, a common difficulty in examining observational studies. Further, the differences across studies in both the timeframe and definition of the outcome of psychosis resulted in a lack of studies that could be quantitatively synthesised, precluding meta-analysis. Nevertheless, the review was instrumental in identifying the key gaps in the literature in this area and was of direct clinical relevance and interest.

Limitations of the studies in Chapters 7-8 relate to a cross-sectional study design, impacting on capacity to draw inferences regarding direction of association and causality; and limited ability to control for a range of factors that could be considered potential confounders for the relationship between methamphetamine use, psychotic symptoms and cognition (such as premorbid IQ). A relatively homogenous and heavy pattern of methamphetamine use in the target sample (50.5% reported daily use in the past month) also limits the generalizability of our findings to individuals who use less frequently.

Nevertheless, this remains one of the largest studies to date of cognition in methamphetamine-using adults. Key strengths of this study include the use of a structured diagnostic interview (SCID I/P)(30) to systematically identify and exclude participants with a history of pre-existing psychotic disorder. Indeed, of the 13 studies included in the systematic review (Chapter 6) only three other studies (36, 42, 51) screened out participants with pre-existing psychotic illness using diagnostic interviews. The exclusion of participants with schizophrenia or other psychotic disorders ensures that the assessment of psychotic symptoms in this study was due to MAP, rather than other psychiatric illness. Further strengths were the naturalistic study design which did not exclude participants who used multiple substances, as this is representative of clinical populations in Australia and internationally. Psychotic symptoms were assessed using a widely used and validated instrument (Brief Psychiatric Rating Scale), administered by specifically trained researchers with postgraduate qualifications and clinical experience. These factors therefore support the strength of our findings whilst highlighting the need for more research.

10.8. Future Research Directions

The studies in this thesis provided novel perspectives into the utility of cognition as a correlate and potential marker of psychotic symptoms in people who use methamphetamine. The work in this thesis suggests the need for the following key future research directions.

10.8.1. Prospective longitudinal study design

In the studies in this thesis, we did not prospectively follow-up participants over time, and consequently, were unable to ascertain the direction of the association between FER and psychotic symptoms. This is a critical question that can only be answered by further longitudinal research. While a significant limitation of this work, this also applies to the majority of available studies in this field. For instance, of the 12 studies identified in the systematic review

of correlates of methamphetamine-associated psychosis in this thesis (Chapter 6), only one (42) incorporated prospective longitudinal follow-up of participants in the study design. Prospective longitudinal studies of substance use cohorts are rare and can be significantly impacted on by loss to follow-up, attrition as a result of physical and mental health co-morbidity, and itinerancy or chaos arising from a lifestyle associated with dependent use of illicit substances. Nevertheless, in order to build an accurate understanding of whether FER represents a potential vulnerability marker of psychosis risk in methamphetamine use populations, larger scale longitudinal research is essential. Future research could follow-up methamphetamine-using participants from baseline prospectively, examining changes in FER in the context of variation in MA use and variation in psychotic symptoms. This would allow analysis of whether FER performance remains stable for the individual over time, or whether it is sensitive to changes in MA use and/or psychotic symptoms. Outcomes of such research could provide useful information as to whether FER impairment comprises a 'state' or 'trait' phenomenon in MAP, similar to the approach utilized in studies of primary psychotic disorder (174).

10.8.2. Comprehensive assessment of FER and other aspects of Social Cognition

This thesis only examined one aspect of social cognition, recognition of facial emotional expression. There is a wide range of processes involved in social cognition that have yet to be explored in the context of MAP or any other substance-induced psychotic disorder, including the role of attributional bias and Theory of Mind. Impairment across these different domains has been found in schizophrenia (212) and bipolar disorder (213). As such, the discovery of impairment across different types of social cognition would add weight to the possibility that MAP shares a similar neurobiological construct to other psychotic disorders. Further, the discovery of other social cognitive impairments in MAP and/or MA dependence may lead to new treatment approaches. For instance, social cognition and interaction training (SCIT) is being explored as a novel means of addressing deficits in social cognition in people with schizophrenia (152).

10.8.3. MAP, social cognition, violence and hostility

MA use is related to violence and hostility, and the findings of this thesis have implications for how the relationship between MA, psychotic symptoms and violence is understood. Methamphetamine use has been found to directly increase the risk of violent behaviour in a dose-dependent manner, independently of the experience of psychotic symptoms (214). In their study of 278 MA-dependent participants, McKetin and colleagues found that over half the participants (51%) self-reported violent behaviour in the past month on at least one of four time-

points of assessment of the three-year study. Their findings supported a causal relationship between MA use and violent behaviour, over and above the effect of psychotic symptoms, as well as pre-morbid risk factors for violence and social adversity.

In contrast, in their study of 237 people with injecting MA use, Lapworth and colleagues identified that hostility was driven by positive psychotic symptoms, in combination with trait impulsivity (179). They demonstrated that impulsivity and positive psychotic symptoms interacted to contribute to a greater degree of hostile behaviour than that predicted by each variable alone. They put forward the theory that positive psychotic symptoms led to interpretation of the environment as threatening, and that combined with a lack of inhibition and control, this led to increased hostility.

In their 2009 review, Dawe and colleagues discussed potential mechanisms by which amphetamine use could be linked with hostility and violence. They suggested that sub-threshold positive psychotic symptoms could lead to misinterpretation of threat, resulting in individuals responding pre-emptively in an aggressive manner to benign social stimuli (215). This is a theory that has been suggested by other authors to explain the relationship between positive psychotic symptoms and agitation in non-drug related psychosis (200). In this literature, social cognition has been considered as a potential explanatory mechanism underpinning misinterpretation of threat and raising the risk of hostility and violence (200).

The findings of this thesis could add to the literature on MAP and violence by providing a mechanism by which both MA use and positive psychotic symptoms contribute to threat misinterpretation in MA dependence; that is, through impaired FER. In our sample, generalised impairment in FER was observed across the group in comparison with healthy controls (Chapter 8), and that methamphetamine-using people with clinically significant past month positive psychotic symptoms had specific difficulties in recognition of anger (Chapter 7).

These findings are consistent with the findings by Dawe, Lapworth and others, suggesting that impairments in FER could potentially serve as a mechanism by which MA dependence and positive psychotic symptoms elevate the risk of hostility. However, our study did not directly assess hostility or aggression, and so this remains a theoretical explanation of this association. Future research aiming to unpack the relationship between MA use and aggression could focus on elucidating the role of both FER impairment and other aspects of social cognition in

mediating this.

10.8.4. MAP, SOCIAL COGNITION AND TRAUMA

A missing link in the understanding of the relationship between FER and MAP is the role of trauma. There is emerging evidence that deficits in FER are found in a greater proportion of individuals with psychotic disorders who have a history of childhood sexual trauma, compared to individuals without a history of sexual abuse (216, 217). In one study of a group of adults with schizophrenia, authors found that people without a history of sexual trauma were able to identify both their own emotional state, and that of others (217). However, those with a history of childhood sexual abuse, whilst still able to recognise and label their own emotions, struggled to correctly identify emotions in others. This interesting finding points to the potential role of childhood trauma in driving deficits in emotion recognition and social cognition that are found in people with psychotic disorders.

The systematic review (Chapter 6) found only one study that examined childhood trauma as a correlate of MAP. Ding and colleagues study identified that methamphetamine-dependent individuals with a history of adverse childhood experiences had up to 4.5 times greater odds of experiencing MAP in their lifetime. They also found a 'dose-response' or graded relationship between the number of adverse childhood experiences and the likelihood of MAP, which remained significant after controlling for MA use, other drug use, and sociodemographic variables (101). However, the study did not include any assessment of social cognition or FER, so it is unclear if the relationship between childhood trauma and MAP may have been potentially accounted for by deficits in FER.

In summary, there remains a gap in the current literature in the study of the association between childhood trauma, deficits in emotion recognition/ FER, and MAP symptoms.

10.8.5. SOCIAL COGNITION AS A TREATMENT TARGET

A further avenue of future inquiry is the evaluation of the utility of social cognition as a potential therapeutic target in MAP and methamphetamine dependence. In the schizophrenia literature, impairment in FER has been found to robustly predict functional outcomes, over and above other neurocognitive measures (122). Social cognition is increasingly recognised as a viable and promising treatment target in schizophrenia as remediation in social cognitive deficits has been shown to translate to improvement in real-world functional outcomes (151, 218). There is emerging evidence demonstrating that targeted emotion recognition training can improve performance on tasks of FER in adults with schizophrenia, and that this may relate to

improvement in function (152). What remains unknown is whether addressing FER impairment also addresses the underlying process of psychosis, or psychosis risk. There have been no studies examining FER as a target to reduce the risk of transition to psychotic disorder in UHR cohorts, for example.

A domain for future research could be the assessment of FER impairment in relation to both functional and treatment outcomes in methamphetamine-dependent populations, with the possibility of interventions targeted at improvement in interpersonal function, social connection, and enhancement of recovery. Social cognition interventions could also target hostility in people with MAP. For instance, a study by Combs and colleagues found that social cognition remediation training in people with schizophrenia resulted in a reduction in the number of aggressive incidents (152), raising the potential of similar interventions reducing hostility risk in other types of psychotic illness.

10.8.6. Clinical Implications

There are a number of key findings of this thesis that are of potential relevance for clinicians, and for the alcohol and other drug (AOD) and mental health treatment sector.

Firstly, we found that MA frequency and severity of dependence to be consistently associated with the likelihood of MAP in our systematic review (Chapter 4). The results of our review highlight the need for MA frequency and severity to be a key target of interventions that address MAP, emphasizing that it is critical for evidence-based care for MA dependence to be central to the treatment of MAP in both mental health and AOD treatment settings. While pharmacological treatment approaches have not shown to be effective in treating MA dependence to date (219), there is substantial evidence supporting the efficacy of psychological and behavioural treatments such as cognitive behavioural therapy, contingency management or structured psychosocial therapies like the MATRIX model (220). Standard alcohol and other drug (AOD) care in Australia incorporates these psychological treatments and has been shown to work, with primary methamphetamine users having amongst the highest rates of 'treatment success' (reducing or ceasing drug use) compared to people with other primary drugs of concern (221). However, there remain numerous challenges in disseminating this message, in order to break down stigma and engage and retain methamphetamine-dependent individuals in treatment (222).

Secondly, the identification of emotion recognition deficits in MAP could impact on how

clinicians assess and treat the disorder, with assessment of FER and social cognition potentially becoming part of the repertoire of tools available to the frontline clinician. This thesis provides preliminary evidence only, and prospective research is needed to identify whether FER impairment presents a vulnerability marker for psychosis in methamphetamine-use populations. Nevertheless, measurement of FER and social cognition is simple, feasible, acceptable and low-cost and could potentially be easily translated across treatment settings if this proves to be useful.

Thirdly, our finding of specific difficulties in recognition of anger in methamphetamine-using individuals with psychotic symptoms (Chapter 7) has clear implications for how clinicians manage and intervene in people with acute MAP. As discussed in Chapter 6, these results could inform de-escalation and aggression management techniques in the context of MAP in acute health services, suggesting the need to pay specific attention to non-verbal communication given that patients may misinterpret threat or anger cues. More broadly, further research into social cognition in MAP and its relationship to hostility and aggression could lead to potential structural, psychological and pharmacological therapies to address the important problem of methamphetamine-related violence.

Finally, our finding that impairment in emotion recognition is associated with positive psychotic symptoms raise the potential that MAP is part of the same continuum of psychotic experiences as that of primary psychotic disorders, and that it is not, in fact, a separate or independent construct. This has nosological implications for how we understand MAP but may also have consequences for conceptualizing the model of care for MAP and other substance-induced psychotic disorders. For instance, people with first presentations of non-drug related psychosis are captured within a comprehensive, wrap-around, early intervention model of care that has been demonstrated to significantly improve longer term outcomes and minimize persistence of disabling psychotic symptoms. Given that up to a third of individuals hospitalized with a methamphetamine-induced psychotic disorder go on to develop schizophrenia, the findings of this thesis adds a voice to the call for early intervention approaches for MAP, and for the provision of integrated care across substance use and mental health services (223).

Conclusions

Methamphetamine-related psychotic symptoms present a significant burden on acute health services and are common in treatment seeking populations. The studies in this thesis investigated the correlates of MAP, resulting in a range of key findings.

MAP was found to exert a substantial burden on acute ambulance services in Victoria, comparable to primary psychotic illness, with a high prevalence of MAP even in high-functioning individuals presenting early to specialist AOD treatment settings. These studies provided important data on the epidemiology and significance of mental health harms in the local context. In consolidating the evidence on correlates of MAP, we found that it was MA use itself that was the strongest factor associated with the problem across the existing literature. The results of our review were of direct clinical relevance and interest and highlighted the need for provision of evidence-based and targeted treatment of MA use factors as a critical part of the treatment of MAP.

Our investigation of cognitive and social cognitive correlates of MAP led to a novel finding of a relationship between facial emotion recognition and psychotic symptoms in methamphetamine-using individuals, compared to those who used and didn't have psychotic symptoms, and healthy control participants. While this presents preliminary evidence in this area, the lens through which this result is viewed could inform future research directions and clinical implications. From an alcohol and other drug treatment perspective, the recognition of FER impairment in MAP could directly translate to changes in both assessment and treatment processes in mainstream AOD settings, particular if future research clarifies targeted interventions that could improve symptoms of MAP or reduce MAP risk. From a mental health perspective, this interesting finding will lead to further research into the commonalities between MAP and primary psychotic disorders, exploring whether psychosis proneness in MAP is similar to vulnerability for schizophrenia. In addition, our findings suggest that treatment approaches should incorporate the knowledge that individuals with MAP have specific difficulties in understanding and relating to people around them and should explore how this may impact on a person's capacity to connect with others around them or to engage in their recovery.

In conclusion, this thesis comprises a range of work that opens up new avenues of inquiry into how we conceptualize, assess and treat psychotic symptoms in people who use methamphetamine.

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