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Differences in the symptom profile of methamphetamine-related psychosis and primary psychotic disorders

Running title: Methamphetamine use and psychosis

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ABSTRACT

We examined the lifetime experience of hallucinations and delusions associated with transient methamphetamine-related psychosis (MAP), persistent MAP and primary psychosis among a cohort of dependent methamphetamine users. Participants were classified as having (a) no current psychotic symptoms, (n = 110); (b) psychotic symptoms only when using methamphetamine (transient MAP, n = 85); (c) psychotic symptoms both when using methamphetamine and abstaining from methamphetamine (persistent MAP, n = 37), or (d) meeting DSM-IV criteria for lifetime schizophrenia or mania (primary psychosis, n = 52). Current psychotic symptoms were classified as a score of 4 or more on any of the Brief Psychiatric Rating Scale items of suspiciousness, hallucinations or unusual thought content in the past month. Lifetime diagnoses and psychotic symptoms were assessed using the Composite International Diagnostic Interview. Transient MAP was associated with persecutory delusions and tactile hallucinations (compared to the no symptom group). Persistent MAP was additionally associated with delusions of reference, thought interference and complex auditory, visual, olfactory and tactile hallucinations, while primary psychosis was also associated with delusions of thought projection and passivity. The presence of non-persecutory delusions and hallucinations across various modalities is a marker for persistent MAP or primary psychosis in people who use methamphetamine.

Keywords: street drugs, central nervous system stimulants, amphetamine, amphetamine-related disorders, psychotic disorders, paranoia, hallucinations

1 INTRODUCTION

Illicit methamphetamine use (often termed ‘speed’, ‘ice’ or ‘crystal meth’) is a growing public health and social concern (Degenhardt et al., 2014). Globally, between 13.9 million and 53.4 million people are estimated to use amphetamines (0.3 – 1.0% past year use for 15-64 year olds; (United Nations Office on Drugs and Crime, 2015)) and an estimated 17.2 million people are dependent on these drugs (Degenhardt et al., 2014).

A significant public health concern associated with methamphetamine use is an increased risk of psychosis (McKetin et al., 2013) (Callaghan et al., 2012). Methamphetamine use can produce a transient psychotic reaction, characterized by persecutory delusions and hallucinations, which is described as being very similar to acute paranoid schizophrenia (Angrist and Gershon, 1970; Bell, 1973). The drug also compounds risk factors for psychosis that are over-represented amongst people who use it (Farnia et al., 2016), including elevated rates of schizophrenia (Sara et al., 2015), where methamphetamine can precipitate and exacerbate acute psychotic episodes (Curran et al., 2004).

Differentiating between methamphetamine-related psychotic reactions (MAP) and primary psychotic disorders is difficult (Bramness et al., 2012; Mathias et al., 2008; Medhus et al., 2013). At a diagnostic level, this distinction is based almost entirely on the duration of the psychosis. For example, the DSM-5 indicates that a substance-induced psychosis should occur soon after intoxication and not persist for a substantial amount of time (e.g., about one month) after substance use (American Psychiatric Association, 2013). Despite these diagnostic guidelines, a proportion of people who seemingly develop MAP have symptoms that persist for a month or longer (Chen et al., 2015; Chen et al., 2005; Lecomte et al., 2013), or symptoms that recur in the absence of recent methamphetamine use (Sato, 1992; Sato et al., 1983). It is unclear whether these cases of persistent MAP reflect a prolonged psychotic reaction (Tomiyama, 1990) or the precipitation of a primary psychotic disorder in vulnerable

individuals (Callaghan et al., 2012; Chen et al., 2015; Chen et al., 2005; Niemi-Pynttari et al., 2013; Sato, 1992; Schuckit, 2006).

Clinical markers that can identify individuals at risk of experiencing persistent psychosis following methamphetamine use are needed, as these individuals would benefit from an early intervention approach for psychosis to reduce the risk of recurrent psychotic episodes or the development of a chronic psychotic disorder (Rounsaville, 2007). Studies attempting to differentiate MAP from primary psychotic disorders have failed to find consistent differences in the symptom profile, although most examine broad symptom categories (e.g., presence of hallucinations, delusions, affective symptoms) or symptom severity (e.g., severity of positive vs. negative symptoms) (Hides et al., 2015; Medhus et al., 2013; Srisurapanont et al., 2011; Tomiyama, 1990). Even fewer studies have attempted to differentiate the acute from the persistent form of MAP. Aside from a family history of schizophrenia (Chen et al., 2005), risk factors that have been identified (younger age, comorbid mental disorders (Chen et al., 2003; Lecomte et al., 2013; McKetin et al., 2016)) may be incidental correlates of heavy methamphetamine use and/or psychosis (e.g., anxiety disorders, gender), limiting their utility as prognostic markers. However, the findings of Tomiyama (1990) suggest that persistent MAP is a distinct clinical entity from schizophrenia, characterized by greater affective responsiveness, suggesting that there is merit in distinguishing between persistent and transient forms of MAP when looking for vulnerability markers.

An under-explored possibility is whether the types of hallucinations and delusions that people experience could help identify individuals at risk of experiencing persistent psychosis following methamphetamine use. Tsuang et al. (1982) found that substance-related psychoses that persisted beyond 6 months had a clinical profile more similar to schizophrenia than that associated with shorter substance-related psychoses, in that they were more likely to be associated with Schneiderian first-rank symptoms (i.e., complex auditory hallucinations,

delusions of perception, delusions of thought insertion/withdrawal/broadcasting, delusions of passivity (Schneider, 1959)). Rates of auditory hallucinations and affective symptoms were similarly high in both groups, while there was a non-significant trend toward a higher prevalence of visual hallucinations associated with brief substance-related psychosis. No studies have explored this possibility in the context of MAP.

In the current study, we compared the types of hallucinations and delusions experienced by individuals who had transient and persistent psychotic symptoms related to the use of methamphetamine (transient and persistent MAP), and examined how these differed from psychotic symptoms experienced by methamphetamine users with a primary psychosis (schizophrenia or mania). We hypothesized that transient MAP would be characterized specifically by persecutory delusions, whereas persistent MAP, if it was a reflection of precipitated schizophrenia, would be characterized by a more complex symptom profile (including Schneiderian symptoms), and that it would be more similar to the symptom profile seen among methamphetamine users with a primary psychosis. We also compared the prevalence of hallucinations across various modalities to see whether there was any difference in visual, or other non-auditory, hallucinations between these groups, given trends found in the Tsuang et al. (1982) study, and because various types of hallucinations have been associated with organic psychosis (Ali, 2011).

2 METHOD

2.1 Participants and procedure

Participants were selected from a larger study, the Methamphetamine Treatment Evaluation Study (MATES), which is detailed elsewhere (McKetin et al., 2012). From the MATES cohort (n = 501), 17 participants were excluded because they did not meet DSM-IV criteria for methamphetamine dependence on recruitment, 144 were excluded because diagnostic

information was not available for lifetime schizophrenia and mania (i.e., these participants did not partake in the follow-up interviews when diagnoses were made), and 10 were excluded because they had not used methamphetamine during any of the one-month observation periods used in the current study.

All participants provided informed consent, were volunteers, and were reimbursed for their time and travel expenses (up to AUD40 per interview). A structured interview schedule was administered at baseline, and at 3 months, 1 year and 3 years after the baseline interview. Interviews were conducted face-to-face or by phone. All participants in the current analysis were re-interviewed at 3 months and 1 year after entry to the cohort, and 82% (n = 260) were interviewed at 3 years. The current study used data on drug use and psychotic symptoms in the past month at each of these four time points, totaling 1,217 months of data for all of the participants combined.

2.2 Measures

2.2.1 Definitions of transient MAP, persistent MAP and primary psychosis

Lifetime diagnoses of schizophrenia and mania were made at the three month follow-up using the Composite International Diagnostic Interview (CIDI) Version 2.1 (Andrews and Peters, 1998). Psychotic symptoms in the past month were assessed at each time point and defined as a score of four or greater on any of the Brief Psychiatric Rating Scale (BPRS) items of suspiciousness, unusual thought content or hallucinations. BPRS scores of 4 or greater indicate clinically significant or pathological symptom intensity (Lukoff et al., 1986).

We divided participants into four exclusive groups:

- (a) No current symptoms (n = 110): participants who experienced psychotic symptoms neither during months when they were using methamphetamine nor during months when they were not using methamphetamine.

- (b) Transient MAP (n = 85): participants who experienced psychotic symptoms during at least one month when they were using methamphetamine, but not during any months when they were not using the drug.
- (c) Persistent MAP (n = 37): participants who experienced psychotic symptoms during at least one month when they were using methamphetamine and also during at least one month when they were not using the drug.
- (d) Primary psychosis (n = 52): participants who met DSM-IV criteria for a lifetime schizophrenia (n = 10) or lifetime mania (n = 37) or both (n = 5).

The no current symptom, transient MAP and persistent MAP groups excluded participants who met DSM-IV criteria for lifetime schizophrenia or lifetime mania, who had used methamphetamine on all of the follow-ups (because we could not confirm the absence of psychotic symptoms during periods of abstinence from methamphetamine, n = 35), or who had psychotic symptoms only during months of abstinence from methamphetamine (n = 11).

Ratings were made by interviewers (Honours level psychology graduates or equivalent) trained in both the BPRS and the CIDI. Weekly meetings were held to review BPRS ratings in order to maintain inter-rater agreement and avoid rater drift (Ventura et al., 1993). Inter-rater agreement for the definition of psychotic symptoms used in this study was 93%, yielding a kappa of 0.86 (McKetin et al., 2013).

2.2.2 Lifetime delusions and hallucinations

Lifetime delusions and hallucinations were based on the schizophrenia section of the CIDI Version 2.1 (Andrews and Peters, 1998) which was administered at the 3 month follow-up interview. Delusions were grouped as persecutory (beliefs about being spied on, talked about or laughed at, followed or plotted against, or secretly tested), thought projection (hearing other people's thoughts; others hearing their thoughts), thought interference (convinced

strange thoughts were being put directly into their mind, or someone could steal their thoughts), passivity (convinced they were under control of a power or force, or felt strange forces working on them, e.g. x-rays or laser beams), reference (believed that they were being sent special messages through television/radio, or a book, newspaper or song was meant only for them), erotomania (believing a stranger was in love with them), jealousy (convinced their partner was being unfaithful) and mind-reading (believed someone was reading their mind). Hallucinations were categorized as complex auditory hallucinations (voices coming from the participant's body; voices commenting on the participant's behavior or discussing the participant; two or more voices talking to each other; the participant having a two-way conversation with voices), other auditory hallucinations, visual hallucinations, olfactory hallucinations, gustatory hallucinations and tactile hallucinations.

2.2.3 Methamphetamine and other drug use

Days of methamphetamine use in the past four weeks was measured at each time point using the Opiate Treatment Index (Darke et al., 1992). Self-reported abstinence from methamphetamine use was confirmed in a sub-sample of the entire MATES cohort, with false reporting of abstinence occurring in only 6% of cases (McKetin et al., 2013). Age of first methamphetamine use, route of methamphetamine administration, and severity of methamphetamine dependence were assessed at baseline. Days of use in the past four weeks was measured at each time point for cannabis, heroin, cocaine, ecstasy, hallucinogens, alcohol and tobacco.

2.3 Statistical analysis

Data were analyzed using Stata SE version 11.2 (Stata Corporation, 2014). All tests were two-sided with significance set at $p < 0.05$. The lifetime prevalence of each symptom was compared between groups using a Pearson's Chi-square test. Three sets of comparisons were

made. First, participants with transient MAP were compared to participants with no current symptoms to determine what lifetime hallucinations and delusions were associated with transient MAP. Second, participants with persistent MAP and primary psychosis were each compared to participants with transient MAP, to establish which hallucinations and delusions were associated specifically with persistent MAP and primary psychosis respectively. Third, participants with persistent MAP were compared to the primary psychosis group, to test whether the lifetime symptom profile associated with these two groups was significantly different.

3 RESULTS

3.1 Characteristics of the sample

Participants (N = 284) had a mean age of 31.6 years (SD = 8.2 years), 71% were male, and 88% were Australian born. All met DSM-IV criteria for methamphetamine dependence on entry to the study; they had used the drug for a mean of 13.2 years (SD = 7.8 years), and 86% had ever injected it. Methamphetamine use occurred during 58% of the observed months (on a median of 8 days, range 1-28 days) with injection the main route of administration (74% of months). Other drug use consisted primarily of tobacco, alcohol and cannabis (89%, 61% and 56% of months respectively). Psychotic symptoms occurred during 42% of all months. Further details on the demographic and clinical characteristics of the sample are published elsewhere (McKetin et al., 2016; McKetin et al., 2013).

3.2 Lifetime hallucinations and delusions associated with transient and persistent psychotic symptoms

The lifetime prevalence of hallucinations and delusions was below 30% for participants who did not report current psychotic symptoms (i.e., the no current symptom group in Table 1),

with the exception of persecutory delusions, which were reported by 62%. Compared to participants in the no current symptom group, participants with transient MAP were significantly more likely to report lifetime persecutory delusions and tactile hallucinations, but not other symptoms (Table 1). Compared to participants with transient MAP, participants with persistent MAP were no more likely to report lifetime persecutory delusions, but they were more likely to report delusions of reference, thought interference, complex auditory hallucinations and hallucinations in various other modalities (visual, olfactory and tactile) (Table 1). Participants with a primary psychosis were similarly more likely to report most of these symptoms (except for visual hallucinations) and also delusions of thought projection and passivity (Table 1); they did not differ significantly from participants with persistent MAP ($p > 0.05$). Details on how these groups participants compared on other clinical and demographics characteristics are published elsewhere (McKetin et al., 2016).

[Tables 1 about here](#)

4 DISCUSSION

We found that the types of hallucinations and delusions experienced by methamphetamine users are potential markers for the persistence of psychosis following methamphetamine use or for a primary psychotic disorder. Transient MAP was specifically associated with persecutory delusions and tactile hallucinations, whereas persistent MAP was additionally associated with non-persecutory delusions (delusions of reference, delusions of thought interference), complex auditory hallucinations, and hallucinations in other modalities (visual, olfactory and tactile). The lifetime symptom profile associated with persistent MAP was not significantly different to that of participants with a primary psychosis.

The differences in lifetime psychotic symptom profiles associated with transient and persistent MAP, and the lack of a significant difference in the symptom profile of persistent MAP and primary psychosis, suggests that persistent MAP may reflect the precipitation of a primary psychotic disorder in vulnerable individuals. This is consistent with our previous argument (McKetin et al., 2016), and that of other researchers (Tsuang et al., 1982), that persistent MAP reflects a clinical entity distinct from transient MAP and which is more similar to schizophrenia. The specificity of Schneiderian first-rank symptoms to persistent MAP and to primary psychosis is also consistent with this notion, as these symptoms are more prevalent among people diagnosed with schizophrenia and they portend worse outcomes for people with psychotic disorders more generally (Rosen et al., 2011). A caveat with this interpretation of the results is that most participants in our primary psychosis group had mania rather than schizophrenia, and this group may have also included individuals with schizoaffective disorder.

Most previous studies have failed to differentiate between MAP and primary psychotic disorders based on their symptom profile (Bramness et al., 2012; Hides et al., 2015; Medhus et al., 2013; Srisurapanont et al., 2011). Our findings suggest that this failure may be because these studies have focused on the symptoms common to both disorders (e.g. persecutory delusions) or general categories of symptoms (e.g. the presence or severity of hallucinations and/or delusions) rather than specific types of delusions or hallucinations, which we show do differ between these conditions. Moreover, few previous studies have differentiated between individuals who experience transient MAP from those with the prolonged form. Grouping transient and persistent MAP together is likely to obfuscate differences in the symptom profile between MAP and schizophrenia because the latter is more similar to schizophrenia. This problem would be compounded by most previous research being situated in a clinical psychiatric setting which would be biased toward sampling individuals with more severe and prolonged forms of MAP.

Persecutory delusions were by far the most common symptom of transient MAP.

Understanding the neurobiological changes in the brain that occur with heavy methamphetamine use may shed light on the etiology of persecutory delusions (Murray et al., 2013). Acute doses of methamphetamine elevate dopamine levels in the mesolimbic cortex, and this has been identified as a critical factor in the etiology of positive psychotic symptoms—these symptoms being alleviated by the administration of antipsychotic drugs that block dopamine activity (Howes and Kapur, 2009). However, repeated exposure to methamphetamine can also alter the expression of proteins in the striatum that are key to various neuro-regulatory functions (e.g. roles in neuroprotection, neuroplasticity, cell cytoskeleton, energy regulation and synaptic vesicles) (Bosch et al., 2015); it can affect the activity and regulation of the major excitatory and inhibitory neurotransmitters, glutamate and gamma-aminobutyric acid (GABA) (Jiao et al., 2015); and, it can have neurotoxic effects on both dopamine and various other neurotransmitter systems (Yu et al., 2015). Such alterations can persist beyond acute methamphetamine use and may couple with elevated dopamine levels during acute methamphetamine intoxication to produce transient methamphetamine-related symptoms, and may also underpin vulnerability to symptoms that occur beyond acute intoxication with the drug (e.g., in response to stress; (Yui et al., 1997).

The dominance of persecutory delusions with transient MAP could also be related to a number of contextual factors that coalesce with heavy methamphetamine use. Paranoid thinking (and hallucinatory experiences) occur on a continuum in the general population (Reeve et al., 2015), and the risk of experiencing these symptoms is increased by sleep deprivation, stress, emotional dysregulation, impairments in analytic reasoning, past trauma, anxiety, negative self-perception and perceived vulnerability (Freeman and Garety, 2014). The high rates of past trauma (Darke et al., 2010) and anxiety disorders (McKetin et al., 2016) seen amongst heavy methamphetamine users would provide a platform that is ripe for the

emergence of paranoid thinking. A sense of persecution would be further exacerbated by people who use the drug often being stigmatized and marginalized within society (Chalmers et al., 2016), and their living within a vulnerable environment, where persecutory ideation may be congruent with legitimate concerns about safety. The heightened affective state of people during intoxication (or drug withdrawal), poor emotional regulation and potential deficits in judgement and reasoning at this point, could lead to the misinterpretation of events and reinforce persecutory ideas. Sleep deprivation, which is a necessary concomitant of stimulant use, is also associated with paranoid thinking and perceptual disturbances (Reeve et al., 2015). This is not to suggest that the neurobiological changes associated with methamphetamine use do not play a role in the development of delusions, but rather that these contextual factors may make people who use methamphetamine particularly vulnerable to persecutory delusions.

The high rate of non-auditory hallucinations is consistent with previous research on organic psychoses (Ali, 2011; Chaudhury, 2010) and is likely to reflect the various etiological mechanisms underpinning hallucinations (e.g., drug toxicity, nutrient deficiency, sleep deprivation, seizures) which may be triggered by heavy methamphetamine use. Reports of tactile hallucinations (e.g., bugs crawling on a person's skin) are particularly characteristic of stimulant use (Ali, 2011), and are likely to be due to elevated dopamine activity and related sleep disturbances (Fenelon et al., 2002). However, the even higher prevalence of non-auditory hallucinations seen in persistent MAP and primary psychosis (relative to transient MAP) suggests that these hallucinations reflect a vulnerability to psychosis in our sample, rather than their being solely related to drug toxicity or other organic factors. That is, although non-auditory hallucinations may be a marker for organic psychosis, their presence should not be taken to preclude a primary psychosis, or vulnerability thereto, when they occur in the context of methamphetamine use. Also, the nature of hallucinations due to organic factors can differ substantially from those typically associated with psychotic disorders, and can also

differ by drug type (Ali, 2011), indicating a need to review the nature of the hallucinatory experience against potential organic causes.

4.1 Limitations and considerations

These results apply to psychotic phenomenon observed among people who use methamphetamine. To identify participants with transient versus persistent MAP we relied on several discrete observation periods, which would have led to misclassification of some participants (e.g., participants may have experienced persistent psychotic symptoms from methamphetamine use, but not during the time-periods captured in our study). Any misclassification would have undermined our capacity to detect associations between the psychotic symptom profile and the persistence of methamphetamine-related psychotic symptoms. The relatively small number of participants classified as having persistent methamphetamine psychosis would have also have reduced our capacity to identify differences between transient and persistent MAP.

Our symptom profile analysis was based on participants' lifetime experiences of hallucinations and delusions rather than their current symptoms. It is not clear whether these same symptom profiles would be mirrored in acute presentations of MAP because our assessment of current MAP was based only on the core symptoms of methamphetamine psychosis (paranoid delusions and hallucinations). Further research will be needed to determine whether the symptom profile in acute presentations of methamphetamine psychosis can be similarly used to predict prognosis, as per previous research examining the prognostic value of other clinical features of substance-related psychosis (Caton et al., 2006; Tsuang et al., 1982).

4.2 Conclusion

MAP patients who present with a history of psychotic symptoms other than persecutory delusions and tactile hallucinations, particularly Schneiderian first-rank symptoms, should be monitored carefully because they may be at elevated risk for recurrent psychotic episodes or the development of a primary psychotic disorder. Further research is needed to confirm whether this symptom profiling has prognostic value in a clinical setting.

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Table 1. Lifetime psychotic symptoms by current psychosis group

	No current symptoms (n = 110)	Transient MAP (n = 85)	Persistent MAP (n = 37)	Primary psychosis (n = 52)	Total sample (N = 284)
Lifetime delusions, n (%)					
Persecutory	68 (62)	71 (84)**	33 (89)	49 (94)	221 (78)
Reference	14 (13)	14 (16)	14 (38)*	21 (40)**	63 (22)
Thought interference	10 (9)	13 (15)	14 (38)**	19 (37)**	56 (20)
Thought projection	17 (15)	22 (26)	12 (32)	22 (42)*	73 (26)
Passivity	13 (12)	11 (13)	10 (27)	14 (27)*	48 (17)
Erotomania	1 (1)	1 (1)	2 (5)	8 (15)**	12 (4)
Jealousy	26 (24)	22 (26)	11 (30)	20 (38)	79 (28)
Mind reading	8 (7)	11 (13)	10 (27)	11 (21)	40 (14)
Lifetime hallucinations, n (%)					
Complex auditory	19 (17)	22 (26)	20 (54)**	27 (52)**	88 (31)
Other auditory	17 (15)	22 (26)	5 (14)	7 (13)	51 (18)
Visual	34 (31)	34 (40)	22 (59)*	26 (50)	116 (41)
Olfactory	15 (14)	19 (22)	15 (41)*	25 (48)**	74 (26)
Gustatory	24 (22)	17 (20)	9 (25)	13 (25)	63 (22)
Tactile	26 (24)	40 (47)**	28 (76)**	34 (65)*	128 (45)

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ Comparisons made relative to no symptom group for transient MAP, and relative to transient MAP for the persistent MAP and primary psychosis groups. No statistically significant differences ($p > 0.05$) existed between the persistent MAP and the primary psychosis groups.