

April 2012

# Methamphetamine-Associated Psychosis

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Grant, Kathleen M.; Le Van, Tricia D.; Wells, Sandra M.; Li, Ming; Stoltenberg, Scott F.; Gendelman, Howard E.; Carlo, Gustavo; and Bevens, Rick A., "Methamphetamine-Associated Psychosis" (2012). *Faculty Publications, Department of Psychology*. 562.  
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# Methamphetamine-Associated Psychosis

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Received: 6 May 2011 / Accepted: 21 June 2011 / Published online: 5 July 2011  
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**Abstract** Methamphetamine (METH) is a frequent drug of abuse in U.S. populations and commonly associated with psychosis. This may be a factor in frequent criminal justice referrals and lengthy treatment required by METH users. Persecutory delusions and auditory hallucinations are the most consistent symptoms of METH-associated psychosis (MAP). MAP has largely been studied in Asian populations and risk factors have varied across studies. Duration, frequency and amount of use as well as sexual abuse, family history, other substance use, and co-occurring personality and mood disorders are risk factors for MAP.

MAP may be unique with its long duration of psychosis and recurrence without relapse to METH. Seven candidate genes have been identified that may be associated with MAP. Six of these genes are also associated with susceptibility, symptoms, or treatment of schizophrenia and most are linked to glutamatergic neurotransmission. Animal studies of pre-pulse inhibition, attenuation of social interaction, and stereotypy and alterations in locomotion are used to study MAP in rodents. Employing various models, rodent studies have identified neuroanatomical and neurochemical changes associated with METH use. Throughout this review, we identify key gaps in our understanding of MAP and suggest potential directions for future research.

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**Keywords** Candidate genes · Drug addiction ·  
Methamphetamine · Psychotic symptoms · Schizophrenia ·  
Substance use disorder

## Introduction

Methamphetamine (METH), a member of the amphetamine family of drugs of abuse, is easily manufactured and readily available in the USA. In 2008, approximately 13,000,000 or 5% of persons age 12 and older in the USA reported having used METH in their lifetime. While this decrease from 6.5% in 2002 (NSDUH 2009) is significant, sub-groups remain particularly vulnerable to METH use disorders (MUD). For example, rural persons are more likely to use the drug than persons in either small or large metropolitan areas; and a recent analysis of the National Survey on Drug Use and Health noted that METH use increased as the setting became more rural (Lambert et al. 2008). Of concern, young adults in rural areas were nearly

twice as likely as their urban counterparts (2.9 versus 1.5%,  $p < 0.001$ ) to have used METH. Additionally, non-Hispanic whites entering Substance Use Disorders (SUD) treatment are most likely to identify opiates and marijuana as their illicit drugs of choice; whereas, Hispanic and Asian Americans are more likely to identify METH/amphetamine as their primary drug of choice (SAMHSA 2009). Lastly, gay and bisexual men use METH at much higher rates than other populations (Shoptaw et al. 2003). Significantly, U.S. youth had the second highest rate of amphetamine use worldwide in 2007 (UNODC 2009). Additionally, persons with METH use disorders entering SUD treatment are more likely to be referred by the criminal justice system than all other SUD admissions combined (59 versus 38%) and over twice as likely to receive long-term residential treatment than all other admissions (17 versus 8%) (SAMHSA 2009). It is unknown why METH use results in greater criminal justice-related admissions or longer treatment stays, but drug-associated psychotic symptoms may have a role in the drug's unique behavioral effects. While amphetamines such as METH can precipitate and exacerbate psychotic symptoms in persons with schizophrenia (Batki and Harris 2004), it has long been recognized that such drug use can produce psychotic symptoms even in persons with no history of a primary psychotic disorder (Chen et al. 2003; McKetin et al. 2006). With these issues in mind, the goals of this review are to describe the risk factors, frequency, symptoms, and clinical implications of METH-associated psychosis (MAP), discuss candidate genes with significant associations, and review preclinical animal research that aims to simulate an understanding of MAP. Within each of these areas, we will discuss gaps in our current knowledge and potential directions for future research.

## Clinical features

### Natural history and epidemiology of MAP

METH, cocaine, cannabis, alcohol, hallucinogens, sedatives, and heroin have all been implicated in substance-induced psychosis (Caton et al. 2005; van Os et al. 2002; Fergusson et al. 2003; Arseneault et al. 2004; Manschreck et al. 1988). Historical features such as psychotic symptoms presenting before onset of substantial substance use or psychotic symptoms only occurring in the context of substance use are useful in establishing a diagnosis. However, in many clinical settings the history is less clear and discriminating between psychoses that are secondary to substance use such as METH and those that are primary psychotic illnesses in a substance-using individual can be diagnostically challenging. In a study of 400 subjects recruited from five psychiatric emergency departments with

at least one psychotic symptom and some substance use in the previous 30 days, 44% of subjects were diagnosed with a substance-induced psychosis while 56% were diagnosed with primary psychosis. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM), which employs the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for psychotic disorders, was utilized to discriminate between substance-induced and primary psychosis. Of note, a diagnosis of primary psychosis was made if there was “no evidence of heavy substance use or withdrawal, when psychotic symptoms persisted for at least 4 weeks in the absence of heavy substance use, or when psychotic symptoms preceded onset of heavy use.” Parental substance abuse, drug dependence (rather than abuse or use), and visual hallucinations were predictive of a substance-induced psychosis. Additionally, persons with substance-induced psychosis had lower Positive and Negative Syndrome Scale (PANSS) scores, greater awareness of psychotic symptoms and were more likely to have suicidal ideation (Caton et al. 2005). Similarly, in a small study ( $N=19$ ) of stimulant (cocaine or amphetamine) abusers seen in an emergency setting with psychotic symptoms determined by the Structured Clinical Interview for DSM-IV, positive rather than negative psychotic symptoms predominated with all participants reporting persecutory delusions, and most having delusions of reference and some form of hallucinations (Harris and Batki 2000). While these studies are useful in characterizing substance use-related psychosis, as will be discussed later in relation to METH, utilizing duration of psychotic symptoms as a key determinant in distinguishing primary psychosis from substance-induced psychosis may not be valid in all clinical settings.

MAP has been most consistently described in Japanese populations typically associated with longstanding METH use and characterized as resembling paranoid schizophrenia. Attempting to distinguish psychiatric disease symptoms that are appropriate to the situations within which METH users typically find themselves (purchasing, using, distributing and/or manufacturing the drug or engaging in other illegal activities), those symptoms which are unmasked by METH use but are related to an underlying psychotic illness (e.g., schizophrenia), and those symptoms which are secondary to the drug itself can be challenging. Nevertheless, a subset of METH users develops frank psychotic symptoms across a range from mild paranoia to hallucinations or unusual thought content.

In previous studies of METH users, Japanese, Taiwanese, Australian, and U.S. investigators have identified factors associated with MAP. In early Japanese studies (published 1955–1992), longer duration and more frequent METH use were associated with MAP (Ujike and Sato 2004). Of note, during this time period, Japanese METH users typically used

METH exclusively in contrast to the poly-drug use seen in typical U.S. METH users (Ujike and Sato 2004). In 2003, Chen characterized three groups of Taiwanese METH users who were either hospitalized or in a detention center: those with no history of any psychotic symptoms, those with brief psychosis (less than 1 month after last METH use), and those with prolonged psychosis (psychosis which persisted more than 1 month after last METH use). In this study, those with MAP had earlier first METH use and used larger amounts of METH than those who had no history of psychotic symptoms. There was no difference in duration of METH use between the psychosis and non-psychosis group. There were, however, significant pre-morbid schizoid/schizotypal personality trait scores in those with METH-associated psychosis, and there was a significant linear correlation between these trait scores and presence and duration of psychosis. Additionally, the psychosis group had greater alcohol dependence, anti-social personality disorder (ASPD), and major depression (MDD) (Chen et al. 2003). In the same population, the first-degree relatives of those with psychosis were more likely to have schizophrenia than those METH users who had never had psychosis (OR=5.4, 95% CI: 2.0–14.7,  $p<0.001$ ). Further, the risk for schizophrenia in the first degree relatives of those with prolonged psychosis was greater than those METH users with brief psychosis (OR=2.8, 95% CI: 1.0–8.0,  $p=0.042$ ). Chen noted that the greater the “familial loading for schizophrenia, the more likely a METH user is to develop psychosis and the longer that psychosis is likely to last” (Chen et al. 2005).

In an Australian study of community METH users, McKetin found that MAP typically occurred in the context of METH abuse or dependence rather than “recreational” METH use. In METH users with no prior history of psychosis, the prevalence of psychosis among dependent users was 27% as compared to 8% in non-dependent users. However, daily METH use, injection use, and socio-demographic factors were not associated with METH psychosis (McKetin et al. 2006). In Japanese and Australian studies, method of METH administration (injection versus smoking) did not affect frequency of psychosis (Matsumoto et al. 2002; McKetin et al. 2008). In a study of adults with METH dependence in SUD treatment in the U.S., sexual abuse, greater frequency of recent METH use, and METH use combined with other drug use were associated with psychotic symptoms (Christian et al. 2007). In another U.S. study ( $N=39$ ) of persons with METH dependence who reported either frequent or infrequent psychosis while intoxicated on METH, there was no difference between the two groups in measures of intelligence, education, age of first METH use, or duration of METH use. However, those with frequent psychosis reported greater childhood attention deficit disorder (ADHD) and family history of psychiatric illness. Of the participants who had a positive

family history for psychiatric illness, 67% had frequent psychotic episodes (Salo et al. 2008). In a small U.S. study ( $N=19$ ) of individuals being seen in an emergency setting, higher quantitative plasma METH and amphetamine levels were associated with more severe psychotic symptoms, but not to reported amounts of METH ingestion (Batki and Harris 2004). These studies did not identify factors which were consistently associated with MAP. However, the variability in the populations studied (e.g. community v. hospitalized), methamphetamine severity (use v. dependence) or use histories (single drug v. poly-drug) may have contributed to this inconsistency.

While METH psychosis has been discussed in the medical literature since the 1950s, previous studies examining the frequency of MAP have employed varying definitions of the disorder. Additionally, not all of the studies used standardized instruments to measure psychotic symptoms or described the time period (e.g., lifetime, current) within which psychosis was examined. Further, many of these studies (written in Japanese) are not accessible to all investigators. However, in a summary article, Sato noted that in previous Japanese studies more than 76% of METH users had a “paranoid psychotic state with hallucinations” (Sato 1992). In a comparison of non-treatment seeking cocaine- and METH-dependent men and women, METH-dependent individuals were more likely to report psychotic symptoms than cocaine-dependent men and women (Mahoney et al. 2008). While noting the above limitations in definition and diagnosis, as well as the variety of populations studied, in recent studies between 26 and 46% of persons with METH dependence have MAP (see Table 1).

### Signs and symptoms of MAP

While it has been difficult to identify factors consistently associated with MAP or to precisely determine the frequency of MAP, the characterization of MAP symptoms across populations has been quite consistent. Multiple studies in Japanese (Akiyama 2006), Taiwanese (Chen et al. 2003), Australian (McKetin et al. 2006), and Thai (Srisurapanont et al. 2003) populations have described with remarkable consistency a high frequency of persecutory delusions and auditory hallucinations in persons with METH-related psychosis. Other frequently reported symptoms were delusions of reference, visual hallucinations, and thought broadcasting (Chen et al. 2003; Srisurapanont et al. 2003; Akiyama 2006). Ujike and Sato contend that there is a progression of MAP with an initial phase of psychotomimetic effects such as stimulation and heightened concentration, followed by “prepsychosis” with delusions, which may then progress to frank psychosis with hallucinations and delusions of reference (Ujike and Sato 2004). In a study of 149 METH users, the average latency from first

**Table 1** Frequency of METH associated psychosis

Population studied	Time period	% Psychotic symptoms	Psychosis definition	Reference
US gay & bisexual treatment-seeking METH abuse/dependent men 18–65 years	Lifetime	26.5%	SCID	Shoptaw et al. 2003
Australian community METH users >16 years	Past Year	13%	BPRS	McKetin et al. 2006
METH dependent		27%		
Non-METH dependent		8%		
Taiwanese incarcerated adolescent METH users	Past Year	7.5%	K-SADS-E	Yen and Chong 2006
U.S. adults in treatment for METH dependence	Lifetime	36%	MINI	Grant et al. 2007
Rural		45%		
Urban		29%		
US METH dependent adults in treatment (didn't distinguish between METH-induced or primary psychotic disorders)	Past or current	12.9%	MINI	Glasner-Edwards et al. 2008
Rural Australian community volunteers >16 years with METH dependence	Lifetime	46%	Self-reported	Wallace et al. 2009
U.S. community and in-treatment METH dependence	Lifetime	45%	MEQ	Leamon et al. 2010

*BPRS* Brief psychiatric rating scale; *K-SADS-E* Kiddie epidemiologic version of schedule for affective disorders and schizophrenia; *MEQ* METHamphetamine experience questionnaire

*MINI* Mini-International neuropsychiatric interview; *SCID* Structured clinical inventory for DSM-IV

use of METH to onset of psychosis was 5.2 years (Ujike and Sato 2004), while a study comparing METH smokers and METH injectors found a latency of 1.7 years in smokers and 4.4 years in injectors (Matsumoto et al. 2002). Severity of psychotic symptoms has been associated with frequency of METH use, METH injection (Zweben et al. 2004), and severity of METH craving (Nakama et al. 2008).

Most episodes of substance-induced and MAP are of brief duration and resolve as substance levels diminish. However, Japanese investigators have reported that while MAP may be transient with recovery within 1 month of last METH use, METH psychosis may also be prolonged, persisting for longer than 6 months (Ujike and Sato 2004), and may persist despite drug abstinence (Akiyama 2006). Western investigators have been more hesitant to attribute persistent psychotic symptoms solely to substance use and this is reflected in the diagnostic lexicon of the Diagnostic and Statistical Manual-IV which defines substance-induced psychosis as persisting for 1 month or less after last substance use (APA 2000). In contrast, in a Japanese study of 104 hospitalized METH users with no prior history of non-METH-related psychosis, 52% of participants' psychotic symptoms abated within 1 week; whereas, in 26% of participants symptoms persisted for more than 1 month and in 16% of participants symptoms persisted for more than 3 months. Symptoms of psychosis were similar between the transient (duration < 1 week) and persistent (duration >

3 months) groups except that persons with persistent psychosis reported greater non-auditory and non-visual hallucinations (Iwanami et al. 1994). In a Taiwanese study of 174 METH users with psychotic symptoms, 17% had psychosis despite being abstinent for more than 1 month (Chen et al. 2003). In both studies, study participants were abstinent and had no history of schizophrenia or prior psychoses. It is unclear if long duration of MAP reflects the drug's ability to cause a chronic psychotic disorder or if METH is unmasking a psychotic disorder in persons with an underlying psychotic diathesis. As previously noted, chronic psychotic symptoms associated with METH are more likely to occur in those with a family history of schizophrenia or in persons with a premorbid schizoid/schizotypal personality (Chen et al. 2003, 2005). Additionally, a previous neurological disorder (head injury, ADHD, prematurity, learning disability) may increase the risk of treatment-resistant psychosis in METH users (Fujii 2002).

Individuals with a brief METH-related psychosis may relapse to MAP with resumption of METH use or with a stressor such as severe insomnia or heavy alcohol use without METH consumption (Sato 1992; Yui et al. 2000; Ujike and Sato 2004). When MAP recurred with re-exposure to METH the symptoms were nearly identical to those in previous psychotic episodes (Sato 1992). If relapse to psychosis follows METH use, it typically occurs promptly with 60% of METH users relapsing in less than 1 week and 80% relapsing within 1 month. Spontaneous

relapse usually occurred in persons with greater than 2 years of METH abuse and vulnerability to relapse provoked by re-use of METH persists for years (Ujike and Sato 2004).

#### Treatment of MAP

In multiple prior studies, the presence of both psychiatric illness and substance use worsened SUD treatment outcome (Rounsaville et al. 1991; Moos et al. 1994; Weisner et al. 2000). In a study of 526 METH dependent adults, individuals with any history of psychotic disorder at the 3-year follow-up were more than twice as likely to have been hospitalized in the previous 12 months, had more total hospitalizations, had greater severity of their psychiatric symptoms, and were more likely to have attempted suicide than participants with no history of psychosis. However, the two groups did not differ in their duration of SUD treatment attendance, treatment retention, or METH use. This study, however, did not distinguish between primary and substance-induced psychosis and those who required hospitalization were not eligible for study enrollment (Glasner-Edwards et al. 2008). Also of note, in a study of paranoia in community and in-treatment METH users, 37% of those persons with paranoia obtained a weapon, 11% used a weapon, and 15% attacked another person (Leamon et al. 2010). Only one randomized controlled trial evaluated anti-psychotics in persons with amphetamine-related psychosis. In this 4-week study, there was no significant difference in clinical efficacy between olanzapine and haloperidol (Leelahanaaj et al. 2005).

#### Needs in clinical research

Studies of risk factors for MAP have largely been done in Japanese, Taiwanese, and Australian populations. It is unknown if findings from these large studies are generalizable to other populations such as those in the U.S. given the likely differences in use patterns, socio-environmental factors, and genetics. A single large study of U.S. METH users examined abuse and METH use characteristics and their association with psychosis. However, there are no studies of factors such as perceived stress or cultural stress which have been identified in other populations as being factors in the development of psychoses. Similarly, there are no studies of any kind assessing protective factors for MAP, which may mitigate against risk factors. Of note, none of the above studies examined sleep deprivation as a factor in the genesis of MAP, a factor that is well-described as a stressor which can result in psychosis. Additionally, there are no studies examining what role preexisting conditions, socio-environmental stressors or protective factors play in the severity, persistence or relapse of MAP. Lastly, little is known about the prevention of persistent and recurrent MAP.

#### Susceptibility genes

MAP is likely a complex genetic disease in which environmental factors interact with multiple polymorphic genes to influence susceptibility. Several studies have reported associations between MAP and genetic variation, including single nucleotide polymorphisms (SNPs), variable number tandem repeats (VNTRs), and insertion/deletions (I/D) (see Table 2). The candidate genes listed in Table 2 were selected based on a wide range of evidence, such as biological function, differential expression in disease, involvement in schizophrenia, which is considered pharmacologically similar to MAP, and findings from animal models. In these studies, allele frequencies were compared in unaffected and affected individuals. Unaffected individuals were generally healthy individuals without a history of psychosis-related disorders. Affected individuals were diagnosed using the ICD-10 or the DSM-IV criteria and were primarily individuals with METH dependence and psychosis (20% of studies reported individuals with METH abuse and psychosis). Of note, several studies consisted of heterogeneous populations that included individuals with and without psychosis. (These populations are annotated as such in Table 2.) Another phenotype often considered in these studies was the clinical course of MAP. The prognosis of MAP varied among individuals, some of whom showed continued psychotic symptoms, even after METH was discontinued. Accordingly, the individuals were categorized based on the duration of the psychotic state after METH discontinuation. Transient psychosis was defined as symptoms that improved within 1 month of METH discontinuation and the start of treatment with neuroleptics; whereas, the prolonged type was defined as psychotic symptoms continuing for more than 1 month after METH discontinuation and the treatment of neuroleptics. The hypothesis-driven studies investigating putative candidate genes and their association with psychosis among METH-dependent individuals are summarized in Table 2. Recognizing the high probability of false-positive associations due to multiple comparisons, we chose to focus on candidate genes with significant associations, i.e.,  $p$  value < 0.001. There were seven genes in this category: D-amino acid oxidase activator, Dystrobrevin-Binding Protein 1, Frizzled 3, Metabotropic Glutamate Receptor 2, 5-Hydroxytryptamine (serotonin) Receptor 1A, Prokineticin Receptor 2, and Glycine Transporter 1.

*D-amino acid oxidase activator (DAOA)* DAOA is the gene encoding the d-amino acid oxidase activator. DAOA is expressed in multiple tissues including the amygdala, caudate nucleus, spinal cord and testes (Chumakov et al. 2002). Although the functional mechanisms of DAOA are not fully understood, DAOA activates D-amino acid oxidase, which oxidizes d-serine, an endogenous ligand

**Table 2** Susceptibility genes associated with METH psychosis

Gene Variant	Ethnicity	Comparison Groups (n)	Genotype (%)		p-value	Reference				
			A				B			
			M/M	M/m			M/M	M/m		
<i>AKT1</i>						(Ikeda et al. 2006)c				
rs3803300	JPT <sup>DSM</sup>	METHA-Psychosis (182)b	34.6	50.0	15.4	28.4	53.5	18.1	0.150	
rs1130214	JPT <sup>DSM</sup>	METHA-Psychosis (182)b	70.3	28.0	1.6	72.0	24.7	3.2	0.970	
rs3730358	JPT <sup>DSM</sup>	METHA-Psychosis (182)b	74.7	23.6	1.6	83.3	15.6	1.1	0.019	
rs2498799	JPT <sup>DSM</sup>	METHA-Psychosis (182)b	22.0	53.8	24.0	27.7	48.3	24.0	0.810	
rs2494732	JPT <sup>DSM</sup>	METHA-Psychosis (182)b	47.3	43.4	9.3	48.5	44.0	7.6	0.590	
rs2498804	JPT <sup>DSM</sup>	METHA-Psychosis (182)b	34.6	50.5	14.8	32.5	47.1	20.4	0.200	
<i>ARRB2</i>										(Ikeda et al. 2007)
rs1045280	JPT <sup>ICD</sup>	METHD-Psychosis (177)a	66.1	30.5	3.4	76.4	22.3	1.3	0.012	
rs2036657	JPT <sup>ICD</sup>	METHD-Psychosis (177)a	72.9	24.9	2.2	79.9	18.9	1.2	0.117	
rs4790694	JPT <sup>ICD</sup>	METHD-Psychosis (177)a	78.0	22.0	0.0	86.0	13.6	0.4	0.017	
<i>BDNF</i>										(Itoh et al. 2005)
132C/T	JPT <sup>ICD</sup>	METHD-Psychosis (189)	92.6	7.4	0.0	90.6	9.4	0.0	0.586	
		METHD-Psychosis/T (94)	92.6	7.4	0.0	90.6	9.4	0.0	0.664	
		METHD-Psychosis/P (66)	93.9	6.1	0.0	90.6	9.4	0.0	0.612	
196G/A	JPT <sup>ICD</sup>	METHD-Psychosis (189)	37.0	50.8	12.2	34.7	53.0	12.4	0.889	
		METHD-Psychosis/T (94)	34.0	56.4	9.6	34.7	53.0	12.4	0.778	
		METHD-Psychosis/P (66)	37.9	45.5	16.7	34.7	53.0	12.4	0.472	
<i>CART</i>										(Morio et al. 2006)
-156A/G	JPT <sup>ICD</sup>	METHD-Psychosis (203)a	46.3	41.4	12.3	48.5	41.2	10.3	0.78	
		METHD-Psychosis/T (105)	44.8	43.8	11.4	43.0	43.0	14.0	0.91	
		METHD-Psychosis (203)a	53.3	39.7	7.0	52.5	39.9	7.6	0.97	
IVS1 +224G/A	JPT <sup>ICD</sup>	METHD-Psychosis/T (103)	52.4	41.8	5.8	55.7	38.0	6.3	0.81	
<i>COMT</i>										(Li et al. 2004)
Va1158Met	CHB <sup>DSM</sup>	METHA-Psychosis (143)	51.7	40.6	7.7	58.2	33.6	8.2	0.380	
<i>COMT</i>										(Suzuki et al. 2006)
Va1158Met	JPT <sup>ICD</sup>	METHD-Psychosis (143)	39.9	45.5	14.7	47.0	42.5	10.5	0.310	
		METHD-Psychosis/T (80)	42.5	45.0	12.5	36.5	46.0	17.5	0.630	
<i>CSNK1E</i>										(Kotaka et al. 2008)
rs135745	JPT <sup>ICD</sup>	METHD-Psychosis (215)a	58.6	36.3	5.1	55.1	36.5	8.4	0.35	
		METHD-Psychosis/T (114)	57.0	37.7	5.3	58.3	36.9	4.8	0.98	
<i>DAOA</i>										(Kotaka et al. 2009)
rs3916965	JPT <sup>ICD</sup>	METHD-Psychosis (209)	56.0	35.9	8.1	51.8	41.4	6.8	0.450	
rs2391191	JPT <sup>ICD</sup>	METHD-Psychosis (205)	54.1	36.1	9.8	51.3	41.2	7.5	0.430	

**Table 2** (continued)

Gene Variant	Ethnicity	Comparison Groups (n)	Genotype (%)				p-value	Reference		
			A		B					
			M/M	M/m	m/m	M/M			M/m	m/m
rs947267	JPT <sup>ICD</sup>	METHD-Psychosis (206)	48.1	41.2	10.7	42.4	46.2	11.4	0.450	
rs778293	JPT <sup>ICD</sup>	METHD-Psychosis (203)	53.7	35.5	10.8	62.4	35.5	2.1	0.0002	
rs3918342	JPT <sup>ICD</sup>	METHD-Psychosis (208)	29.8	47.1	23.1	24.7	56.7	18.6	0.110	
rs1421292	JPT <sup>ICD</sup>	METHD-Psychosis (205)	24.9	43.9	31.2	27.0	51.4	21.6	0.054	(Liu et al. 2006)
<i>DRD1</i>										
rs4532	CHB <sup>DSM</sup>	METHA-Psychosis (135)	73.0	26.0	1.0	71.0	26.0	3.0	0.320	(Chen et al. 2004)
<i>DRD2</i>										
rs1800497	CHB <sup>DSM</sup>	METHA-Psychosis (154)	29.9	51.9	18.2	36.9	48.8	14.3	0.288	(Ujike et al. 2009)
<i>DRD2</i>										
rs1800497	JPT <sup>ICD</sup>	METHD-Psychosis (202)a	41.1	41.6	17.3	37.9	46.7	15.4	0.570	
rs1799732	JPT <sup>ICD</sup>	METHD-Psychosis (202)a	70.8	25.1	4.1	74.4	24.7	0.9	0.110	
rs1801028	JPT <sup>ICD</sup>	METHD-Psychosis (202)a	91.7	8.3	0.0	95.2	4.8	0.0	0.170	(Chen et al. 2004)
<i>DRD3</i>										
rs6280	CHB <sup>DSM</sup>	METHA-Psychosis (150)	50.0	42.7	7.3	50.0	40.9	9.1	0.806	(Ujike et al. 2009)
<i>DRD3</i>										
rs6280	JPT <sup>ICD</sup>	METHD-Psychosis (202)a	49.7	43.1	7.8	51.9	39.0	9.0	0.790	(Chen et al. 2004)
<i>DRD4</i>										
VNTR Exon3	CHB <sup>DSM</sup>	METHA-Psychosis (139)	–	–	–	–	–	–	0.860	(Li et al. 2004)c
<i>DRD4</i>										
VNTR Exon3	CHB <sup>DSM</sup>	METHA-Psychosis (139)	–	–	–	–	–	–	–	
5' VNTR	CHB <sup>DSM</sup>	METHA-Psychosis (142)	49.3	43.0	7.7	46.2	43.5	10.3	0.660	
<i>DRD4</i>										
-512C/T	JPT <sup>ICD</sup>	METHD-Psychosis (202)a	30.1	52.3	17.6	27.0	55.3	17.6	0.820	(Ujike et al. 2009)
<i>DRP-2</i>										
2236T/C	JPT <sup>ICD</sup>	METHA-Psychosis (164)	70.7	27.4	1.8	70.1	27.1	2.7	0.90	(Ujike et al. 2006)
<i>DTNBP1</i>										
rs2619539	JPT <sup>ICD</sup>	METHA-Psychosis (190)	41.0	49.5	9.5	49.236.7	44.6	6.2	0.170	(Kishimoto et al. 2008a)c
rs3213207	JPT <sup>ICD</sup>	METHA-Psychosis (197)	42.7	48.6	8.7	53.2	53.2	10.1	0.710	
rs2619538	JPT <sup>ICD</sup>	METHA-Psychosis (197)	88.8	11.2	0.0	98.4	1.6	0.0	2.5 × 10 <sup>-5</sup>	
<i>ESR1</i>										
rs2234693	JPT <sup>DSM</sup>	METHD-Psychosis (197)a	26.9	45.2	27.9	36.5	44.2	19.3	0.049	(Kishi et al. 2009a)

Table 2 (continued)

Gene Variant	Ethnicity	Comparison Groups (n)		Genotype (%)		Genotype (%)		p-value	Reference		
		B		A		B					
		A	B	M/M	M/m	M/M	M/m				
<i>FAAH</i> Pro129Thr	JPT	METHD-Psychosis (Male, 164)a	Healthy (Male, 164)	25.6	42.7	31.7	34.8	46.3	18.9	0.020	
		METHD-Psychosis (Female, 33)a	Healthy (Female, 33)	33.3	57.6	9.1	45.5	33.3	21.2	0.114	(Morita et al. 2005a)
	JPT	METHD-Psychosis (153)a	Healthy (200)	68.6	28.1	3.3	69.5	29.0	1.5	0.570	
		METHD-Psychosis/T (85)	METHD-Psychosis/P (56)	62.4	34.1	3.5	76.8	21.4	1.8	0.190	(Kishimoto et al. 2008b)c
<i>FZD3</i> rs3757888 rs960914 rs2241802 rs2323019 rs352203 rs880481	JPT	METHA-Psychosis (186)	Healthy (230)	81.2	7.2	1.6	86.1	13.5	0.4	0.260	
		METHA-Psychosis (185)	Healthy (240)	24.3	55.7	20.0	27.9	54.2	17.9	0.660	
	JPT	METHA-Psychosis (181)	Healthy (240)	24.3	53.6	22.1	20.4	51.7	27.9	0.340	
		METHA-Psychosis (186)	Healthy (239)	24.1	54.0	21.9	31.4	49.3	19.2	0.250	
	JPT	METHA-Psychosis (176)	Healthy (192)	27.8	55.7	16.5	33.3	51.1	15.6	0.520	
	JPT	METHA-Psychosis (186)	Healthy (236)	16.1	55.4	28.5	18.2	52.1	29.7	0.970	(Nishiyama et al. 2005)
	JPT	METHA-Psychosis (178)b	Healthy (288)	49.0	42.0	9.0	55.0	39.0	6.0	0.374	
		METHA-Psychosis (178)b	Healthy (288)	31.0	44.0	24.0	28.0	44.0	28.0	0.603	(Kishi et al. 2008)
<i>GCLM</i> s60197536 rs2301022 rs718875 rs3170633	JPT	METHD-Psychosis (160)	Healthy (819)	63.8	33.8	2.4	69.8	27.8	2.4	0.307	
		METHD-Psychosis (160)	Healthy (817)	57.5	34.4	8.1	55.1	38.1	6.8	0.627	
	JPT	METHD-Psychosis (160)	Healthy (819)	63.1	34.4	2.5	69.7	27.0	3.3	0.156	
		METHD-Psychosis (160)	Healthy (819)	57.5	40.0	2.5	65.0	30.5	4.5	0.045	(Morita et al. 2008)c
<i>GLYT1</i> rs2486001 rs2248829 rs2248632	JPT	METHA-Psychosis (204)b	Healthy (210)	51.9	40.2	7.8	66.2	30.0	3.8	0.009	
		METHA-Psychosis (204)b	Healthy (210)	56.7	35.7	4.8	52.4	36.2	11.4	0.048	
	JPT	METHA-Psychosis (204)b	Healthy (210)	58.1	33.3	5.7	53.8	38.6	7.6	0.450	(Tsunoka et al. 2010)
		METHD-Psychosis (196)	Healthy (802)	92.3	7.1	0.6	91.0	8.4	0.6	0.856	
<i>GRM2</i> rs3821829 rs12487957 rs4687771	JPT	METHD-Psychosis (196)	Healthy (802)	54.0	40.0	6.0	43.0	30.3	9.7	0.013	
		METHD-Psychosis (196)	Healthy (802)	51.0	41.8	7.2	37.4	50.0	12.6	0.001	(Koizumi et al. 2004)
	JPT	METHD-Psychosis (Female, 125)	Healthy (Male, 157)	46.4	44.8	8.8	42.7	48.4	8.9	0.819	
<i>GST-MI</i> Del/Non-Del rs947894	JPT	METHD-Psychosis (Female, 32)	Healthy (Female, 43)	75.0	21.9	3.1	48.8	48.8	2.3	0.032	
		METHD-Psychosis (159)	Healthy (199)	74.8	22.6222	2.5	83.9	16.1	0.0	0.013	(Hashimoto et al. 2005)
JPT	METHD-Psychosis/T (94)	Healthy (199)	75.5	23.1	2.1	83.9	16.1	0.0	0.045		

**Table 2** (continued)

Gene Variant	Ethnicity	Comparison Groups (n)	Genotype (%)		p-value	Reference				
			A				B			
			M/M	M/m			M/M	M/m		
5- <i>HIT1A</i> rs6295	JPT <sup>DSM</sup>	Healthy (199)	73.8	3.1	83.9	16.1	0.028	(Kishi et al. 2009c)e		
			46.7	43.1	10.2	57.2	34.8		8.0	0.066
			62.9	31.0	6.1	76.8	21.1		2.1	0.001
<i>HTR2A</i> rs6311	JPT <sup>ICD</sup>	Healthy (802)	30.0	49.0	21.0	32.0	47.0	21.0	0.708	(Tsunoka et al. 2010)
			26.5	48.5	25.0	27.4	48.1	24.5	0.965	
			64.0	34.0	2.0	59.0	33.0	8.0	0.022	
5- <i>HIT1LR</i> S/L	JPT <sup>ICD</sup>	Healthy (197)	62.0	35.0	3.0	59.0	33.0	8.0	0.294	(Ezaki et al. 2008)
			68.0	32.0	0.0	59.0	33.0	8.0	0.021	
			50.7	45.3	4.0	49.2	43.7	7.1	0.442	
<i>MAOA</i> 5' VNTR	CHB <sup>DSM</sup>	METHA- Psychosis	–	–	–	–	–	–	–	(Chen et al. 2007)
			–	–	–	–	–	–	–	
			–	–	–	–	–	–	–	
5' VNTR	JPT <sup>ICD</sup>	Healthy (Male, 153)	–	–	–	–	–	–	–	(Nakamura et al. 2009)
			–	–	–	–	–	–	–	
			–	–	–	–	–	–	–	
941T/G	JPT <sup>ICD</sup>	Healthy (Female, 44)	31.6	57.9	10.5	36.4	40.9	22.7	0.380	
			27.3	54.5	18.2	37.5	62.5	0.0	0.440	
			–	–	–	–	–	–	–	
941T/G	JPT <sup>ICD</sup>	Healthy (Male, 153)	–	–	–	–	–	–	–	NS
			–	–	–	–	–	–	–	
			–	–	–	–	–	–	–	
941T/G	JPT <sup>ICD</sup>	Healthy (Female, 45)	33.0	42.9	23.8	28.9	42.2	28.9	0.890	
			46.1	38.5	15.4	12.5	50.0	37.5	0.240	
			–	–	–	–	–	–	–	
<i>NPY</i> rs16147	JPT <sup>ICD</sup>	Healthy (288)	43.8	45.2	11.0	41.3	44.5	14.2	0.54	(Okahisa et al. 2009)
			49.6	38.0	12.4	34.5	54.0	11.5	0.07	
			24.8	56.8	18.5	31.7	45.4	22.9	0.04	
<i>NPY1R</i> rs7687423	JPT <sup>ICD</sup>	Healthy (284)	21.4	61.6	17.0	23.3	53.8	20.9	0.53	(Okahisa et al. 2009)
			37.4	51.0	11.6	41.1	45.9	13.0	0.642	
			–	–	–	–	–	–	–	
<i>NQO2</i> Pro187Ser	JPT <sup>ICD</sup>	Healthy (207)	–	–	–	–	–	–	–	(Ohgake et al. 2005)
			–	–	–	–	–	–	–	
			–	–	–	–	–	–	–	

Table 2 (continued)

Gene Variant	Ethnicity	Comparison Groups (n)	Genotype (%)				p-value	Reference	
			A		B				
			M/M	M/m	M/m	m/m			
I/D	JPT <sup>ICD</sup>	Healthy (207)	44.4	43.2	12.3	41.1	45.9	13.0	0.886
			28.3	60.0	11.7	41.1	45.9	13.0	0.139
			63.3	27.2	9.5	59.4	35.7	4.8	0.085
			59.3	33.3	7.4	59.4	35.7	4.8	0.655
			66.7	21.7	11.7	59.4	35.7	4.8	0.038
<i>NRG-1</i>									
NRG221533	JPT <sup>ICD/DSM</sup>	METHOD-Psychosis (184)	27.2	56.5	16.3	27.5	50.0	22.5	0.161
NRG241930	JPT <sup>ICD/DSM</sup>	METHOD-Psychosis (183)	76.0	23.5	0.5	79.4	19.6	1.0	0.475
NRG243177	JPT <sup>ICD/DSM</sup>	METHOD-Psychosis (180)	26.7	56.7	16.6	27.4	52.5	20.1	0.530
rs3924999	JPT <sup>ICD/DSM</sup>	METHOD-Psychosis (171)	60.2	33.9	5.8	63.4	32.0	4.5	0.652
<i>OPRD1</i>									
IVS1+ 18G/C	JPT <sup>ICD</sup>	METHOD-Psychosis (170)a	82.4	15.9	1.8	84.6	15.4	0.0	0.097
rs2234918	JPT <sup>ICD</sup>	Healthy (260)	85.7	12.1	2.2	84.6	15.4	0.0	0.044
			80.0	18.2	1.8	84.6	15.4	0.0	0.079
			59.4	37.1	3.5	69.6	27.3	3.1	0.089
			56.0	39.6	4.4	69.6	27.3	3.1	0.063
			65.5	32.7	1.8	69.6	27.3	3.1	0.657
rs465327	JPT <sup>ICD</sup>	Healthy (260)	64.1	31.8	4.1	73.1	23.8	3.1	0.143
			60.4	35.2	4.4	73.1	23.8	3.1	0.078
			67.3	29.1	3.6	73.1	23.8	3.1	0.684
			94.0	6.0	0.0	95.0	5.0	0.0	0.990
			38.0	43.0	19.0	31.0	46.0	22.0	0.430
<i>OPRMI</i>									
IVS1-A4980G	JPT <sup>ICD</sup>	METHOD-Psychosis (138)a	38.0	43.0	19.0	31.0	46.0	22.0	0.430
rs1799971	JPT <sup>ICD</sup>	METHOD-Psychosis (131)a	38.0	43.0	19.0	31.0	46.0	22.0	0.430
<i>OPRMI</i>									
rs1799971	JPT <sup>ICD</sup>	METHOD-Psychosis (128)a	38.0	43.0	19.0	31.0	46.0	22.0	0.43
IVS2+691	JPT <sup>ICD</sup>	METHOD-Psychosis (128)a	57.0	33.0	9.0	66.0	31.0	3.0	0.012
IVS3+5953	JPT <sup>ICD</sup>	METHOD-Psychosis (128)a	75.0	22.0	3.0	75.0	23.0	2.0	0.70
IVS3+6151	JPT <sup>ICD</sup>	METHOD-Psychosis (128)a	79.0	20.0	1.0	86.0	13.0	1.0	0.21
<i>PAL-1</i>									
4G/5G I/D	JPT <sup>ICD</sup>	METHOD-Psychosis (184)	47.3	43.5	9.2	39.9	47.9	12.2	NS
<i>Par-4</i>									
rs2463169	JPT <sup>DSM</sup>	METHOD-Psychosis (167)	55.7	35.3	9.0	50.0	43.5	8.5	0.170
rs2400546	JPT <sup>DSM</sup>	METHOD-Psychosis (167)	61.1	32.3	6.6	58.4	36.3	5.3	0.602
rs17005769	JPT <sup>DSM</sup>	METHOD-Psychosis (167)	59.9	31.7	8.4	53.6	38.6	7.7	0.284

**Table 2** (continued)

Gene Variant	Ethnicity	Comparison Groups (n)	Genotype (%)		p-value	Reference				
			A				B			
			M/M	M/m			M/M	m/m		
rs4842318	JPT <sup>DSM</sup>	METHD-Psychosis (160)	44.4	41.9	13.7	48.9	44.4	6.7	0.020	
rs7305141	JPT <sup>DSM</sup>	METHD-Psychosis (160)	40.6	43.1	16.3	34.3	49.6	16.1	0.310	(Matsuzawa et al. 2007)
<i>PICK1</i>										
rs737622	JPT <sup>ICD</sup>	METHD-Psychosis (178)	37.1	48.9	14.0	40.8	49.1	10.1	0.450	
		METHD-Psychosis/T (100)	38.0	48.0	14.0	40.8	49.1	10.1	0.560	
		METHD-Psychosis/P (78)	35.9	50.0	14.1	40.8	49.1	10.1	0.530	
rs11089858	JPT <sup>ICD</sup>	METHD-Psychosis (178)	80.3	19.1	0.6	82.5	17.0	0.5	0.800	
		METHD-Psychosis/T (100)	81.0	19.0	0.0	82.5	17.0	0.5	0.830	
		METHD-Psychosis/P (78)	79.5	19.2	1.3	82.5	17.0	0.5	0.470	
rs713729	JPT <sup>ICD</sup>	METHD-Psychosis (178)	81.5	16.9	1.7	68.8	28.9	2.3	<0.020	
		METHD-Psychosis/T (100)	83.0	16.0	1.0	68.8	28.9	2.3	<0.030	
		METHD-Psychosis/P (78)	79.5	17.9	2.5	68.8	28.9	2.3	0.140	
rs2076369	JPT <sup>ICD</sup>	METHD-Psychosis (178)	36.0	46.6	17.4	37.6	50.9	11.5	0.250	
		METHD-Psychosis/T (100)	34.0	48.0	18.0	37.6	50.9	11.5	0.300	
		METHD-Psychosis/P (78)	38.5	44.9	16.7	37.6	50.9	11.5	0.410	(Kanahara et al. 2009)
<i>PIK4CA</i>										
rs2072513	JPT <sup>ICD</sup>	METHD-Psychosis (232)	23.3	56.0	20.7	25.8	51.5	22.7	0.62	
		METHD-Psychosis/T (111)	24.3	54.1	21.6	25.8	51.5	22.7	0.91	
		METHD-Psychosis/P (88)	19.3	63.6	17.4	25.8	51.5	22.7	0.15	
rs165862	JPT <sup>ICD</sup>	METHD-Psychosis (232)	23.3	54.3	22.4	25.3	50.2	24.5	0.68	
		METHD-Psychosis/T (111)	23.4	54.1	22.5	25.3	50.2	24.5	0.80	
		METHD-Psychosis/P (88)	22.7	55.7	21.6	25.3	50.2	24.5	0.68	
rs165793	JPT <sup>ICD</sup>	METHD-Psychosis (232)	36.5	50.4	12.5	37.1	45.9	15.5	0.52	
		METHD-Psychosis/T (111)	35.1	53.1	11.7	37.1	45.9	15.5	0.41	
		METHD-Psychosis/P (88)	38.6	48.9	12.5	37.1	45.9	15.5	0.78	
rs165789	JPT <sup>ICD</sup>	METHD-Psychosis (232)	23.7	54.7	21.6	25.8	50.1	23.6	0.68	
		METHD-Psychosis/T (111)	24.3	55.0	20.1	25.8	50.1	23.6	0.74	
		METHD-Psychosis/P (88)	22.7	55.7	21.6	25.8	50.1	23.6	0.72	(Iwata et al. 2004)
<i>PLAT</i>										
Alu I/D	JPT <sup>ICD</sup>	METHD-Psychosis (185)	25.9	51.9	22.2	26.7	50.7	22.6	NS	
<i>PLG</i>										
Haplotype	JPT <sup>ICD</sup>	METHD-Psychosis (184)	–	–	–	–	–	–	0.75	(Iwata et al. 2004)
<i>PPP3CC</i>										
rs10108011	JPT <sup>ICD</sup>	METHD-Psychosis (128)	45.3	46.9	7.8	46.8	44.9	8.3	0.81	(Kinoshita et al. 2008)

Table 2 (continued)

Gene Variant	Ethnicity	Comparison Groups (n)	Genotype (%)				p-value	Reference		
			A		B					
			M/M	M/m	m/m	M/M			M/m	m/m
rs2461491	JPT <sup>ICD</sup>	METHD-Psychosis (128)	26.6	53.1	20.3	30.9	49.1	20.0	0.92	
rs2461490	JPT <sup>ICD</sup>	METHD-Psychosis (128)	32.8	56.3	10.9	37.4	49.4	13.2	0.36	
rs2449340	JPT <sup>ICD</sup>	METHD-Psychosis (128)	34.4	53.9	11.7	42.3	46.0	11.7	0.99	
rs1116085	JPT <sup>ICD</sup>	METHD-Psychosis (128)	27.3	52.3	20.3	27.2	51.7	21.1	0.79	(Kishi et al. 2010)c
<i>PROKR2</i>										
rs17721321	JPT <sup>ICD</sup>	METHD-Psychosis (199)a	85.4	14.6	0.0	86.6	12.8	0.6	0.47	
rs6085086	JPT <sup>ICD</sup>	METHD-Psychosis (199)a	38.7	48.7	12.6	54.9	35.9	9.2	0.001	
rs3746684	JPT <sup>ICD</sup>	METHD-Psychosis (199)a	30.0	48.0	22.0	32.6	45.4	22.0	0.750	
rs3746682	JPT <sup>ICD</sup>	METHD-Psychosis (199)a	46.0	42.0	12.0	36.0	46.0	18.0	0.042	
rs4815787	JPT <sup>ICD</sup>	METHD-Psychosis (199)a	30.7	54.7	14.6	47.0	42.0	11.0	0.001	(Liu et al. 2004)
<i>SCL6A3</i>										
3' VNTR	CHB <sup>DSM</sup>	METHA-Psychosis/T (88)	–	–	–	–	–	–	> 0.05	
		METHA-Psychosis/P (28)	–	–	–	–	–	–	> 0.05	
<i>SCL6A3</i>										
3' VNTR	JPT <sup>ICD</sup>	METHD-Psychosis (124)	84.7	14.5	0.8	86.3	12.5	1.3	0.630	(Ujike et al. 2003)
		METHD-Psychosis/T (66)	92.4	7.6	0.0	74.5	23.4	2.1	0.017	
242C/T	JPT <sup>ICD</sup>	METHD-Psychosis (103)	98.1	1.9	0.0	98.1	1.9	0.0	0.970	
		METHD-Psychosis/T (54)	96.3	3.7	0.0	100	0.0	0.0	0.190	
I342A/G	JPT <sup>ICD</sup>	METHD-Psychosis (124)	81.5	17.7	0.8	81.1	16.4	2.5	0.800	
		METHD-Psychosis/T (66)	83.3	16.7	0.0	76.6	21.3	2.1	0.500	
2319G/A	JPT <sup>ICD</sup>	METHD-Psychosis (124)	55.6	38.7	5.6	58.6	36.3	5.1	0.880	
		METHD-Psychosis/T (63)	57.1	38.1	4.8	51.1	42.6	6.4	0.580	(Inada et al. 2004)
<i>SIGMAR1</i>										
GC-241-240TT	JPT <sup>ICD</sup>	METHD-Psychosis (118)	47.5	42.4	10.2	49.7	43.1	7.2	0.660	
Gln2Pro	JPT <sup>ICD</sup>	METHD-Psychosis (118)	41.5	46.6	11.9	47.0	45.4	7.7	0.390	(Aoyama et al. 2006)
<i>SLC22A3</i>										
rs509707	JPT <sup>ICD</sup>	METHD-Psychosis (210)a	43.8	44.3	11.9	51.1	39.6	9.3	0.192	
rs4709426	JPT <sup>ICD</sup>	METHD-Psychosis (211)a	28.0	51.2	20.8	37.3	45.0	17.6	0.061	
rs7745775	JPT <sup>ICD</sup>	METHD-Psychosis (207)a	56.0	40.6	3.4	57.9	34.4	7.8	0.055	
rs3106164	JPT <sup>ICD</sup>	METHD-Psychosis (207)a	57.0	35.7	7.2	46.6	45.0	8.4	0.046	
rs3088442	JPT <sup>ICD</sup>	METHD-Psychosis (210)a	32.4	43.8	23.8	25.3	47.5	27.2	0.167	(Kobayashi et al. 2004)
<i>SNCA</i>										
rs1372520	JPT <sup>ICD</sup>	METHD-Psychosis (170)a	84.0	16.0	1.0	88.0	11.0	1.0	0.389	
rs3756063	JPT <sup>ICD</sup>	METHD-Psychosis (170)a	82.0	17.0	1.0	88.0	11.0	1.0	0.263	

**Table 2** (continued)

Gene Variant	Ethnicity	Comparison Groups (n)	Genotype (%)		Genotype (%)		p-value	Reference		
			A		B					
			M/M	M/m	m/m	M/M			M/m	m/m
rs2870027	JPT <sup>ICD</sup>	METHD-Psychosis (170)a	35.0	52.0	13.0	34.0	47.0	19.0	0.281	
rs3756059	JPT <sup>ICD</sup>	METHD-Psychosis (170)a	83.0	17.0	1.0	88.0	11.0	1.0	0.323	
TA10A7	JPT <sup>ICD</sup>	METHD-Psychosis (170)a	–	–	–	–	–	–	0.677	
<i>SOD2</i>										(Yoshikawa et al. 2006)
rs2758357	JPT <sup>ICD</sup>	METHD-Psychosis (113)	66.4	31.9	1.8	69.9	25.3	4.8	0.220	
		METHD-Psychosis/T (66)	69.7	30.3	0.0	69.9	25.3	4.8	0.161	
		METHD-Psychosis/P (47)	61.7	34.0	4.3	69.9	25.3	4.8	0.481	
rs4880	JPT <sup>ICD</sup>	METHD-Psychosis (116)	72.4	25.9	1.7	80.4	17.5	2.1	0.211	
		METHD-Psychosis/T (68)	80.9	19.1	0.0	80.4	17.5	2.1	0.468	
		METHD-Psychosis/P (48)	60.4	35.4	4.2	80.4	17.5	2.1	0.014	
rs2855116 +										
rs2758332	JPT <sup>ICD</sup>	METHD-Psychosis (116)	78.5	20.7	0.9	81.0	17.5	1.6	0.689	
		METHD-Psychosis/T (68)	83.8	16.2	0.0	81.0	17.5	1.6	0.555	
		METHD-Psychosis/P (48)	70.8	27.1	2.1	81.0	17.5	1.6	0.304	
rs2758330	JPT <sup>ICD</sup>	METHD-Psychosis (115)	30.4	46.1	23.5	26.0	44.9	29.2	0.497	
		METHD-Psychosis/T (68)	28.0	45.6	26.4	26.0	44.9	29.2	0.900	
		METHD-Psychosis/P (47)	34.0	46.8	19.2	26.0	44.9	29.2	0.315	
rs2842980	JPT <sup>ICD</sup>	METHD-Psychosis (115)	23.5	46.1	30.4	28.3	44.9	26.7	0.606	
		METHD-Psychosis/T (68)	26.5	45.6	27.9	28.3	44.9	26.7	0.954	
		METHD-Psychosis/P (47)	19.2	46.8	34.0	28.3	44.9	26.7	0.379	
<i>XBPI</i>										(Morita et al. 2005b)
-116C/G	JPT <sup>ICD</sup>	METHD-Psychosis (153)a	47.1	41.8	11.1	40.0	44.0	16.0	0.280	
		METHD-Psychosis/T (85)	49.4	41.2	9.4	46.4	41.1	12.5	0.850	

Definitions: *METH* methamphetamine; *CHB* Chinese; *JPT* Japanese; *DSM-IV or ICD* Diagnostic criteria for METH dependence/abuse/psychosis, *METHD-Psychosis* METH-dependent individual with psychosis; *METHD-Psychosis/T* METH-dependent individual with transient psychosis that improved within 1 month after discontinuance of METH; *METHD-Psychosis/P* METH-dependent individual with prolonged psychosis lasting greater than 1 month after discontinuance of METH; *METHA* METH abuser; *METHA-Psychosis* METH abuser with psychosis; *NS* No significant differences were detected; *M* Major allele; *m* Minor allele.

<sup>a</sup> Population was composed of METH-dependent individuals with and without psychosis

<sup>b</sup> Population was composed of METH-abusers with and without psychosis

<sup>c</sup> Haplotype analysis resulted in p values < 0.005

for the glycine site of the N-Methyl-D-aspartate (NMDA) type glutamate receptor (Chumakov et al. 2002). D-serine levels are low in schizophrenic patients and administration of D-serine has been shown to reduce some of the symptoms of this disease (Kantrowitz et al. 2010). This provides a potential link between DAOA and the glutamate hypo-function hypothesis of schizophrenia, which integrates environmental influences and causative genes, is based on clinical and neuropathological evidence of the hypo-function of glutamatergic signaling via NMDA receptors. The DAOA gene is located on chromosome 13q and has been found to be a susceptibility locus for schizophrenia (Badner and Gershon 2002), and many studies have found an association between genetic variants in DAOA and schizophrenia (Chumakov et al. 2002; Schumacher et al. 2004; Yue et al. 2007). In a case-controlled study, Kotaka et al. (2009) demonstrated an association between a DAOA polymorphism (rs778293;  $p=0.0002$ ) and psychosis among METH-dependent subjects. This polymorphism was previously shown to be associated with schizophrenia; however, its functionality is unknown.

*Dystrobrevin-binding protein 1 (DTNBP1)* DTNBP1 encodes dystrobrevin-binding protein 1 also referred to as dysbindin. This ubiquitously expressed, coiled-coil-containing protein is a subunit of the biogenesis of lysosome-related organelles complex 1 (BLOC-1), which regulates trafficking to lysosome-related organelles (Li et al. 2003). In muscle and non-muscle cells, DTNBP1 binds to  $\alpha$ - and  $\beta$ -dystrobrevins, components of the dystrophin-associated protein complex (DPC) (Benson et al. 2001). In muscle, the DPC is required for the maintenance of muscle integrity and normal muscle function. In the brain, dysbindin is most prevalent in axons, particularly those with large synaptic terminals such as the mossy fiber synaptic terminals in the cerebellum and hippocampus (Benson et al. 2001). In a case controlled study, Kishimoto et al. (2008a) demonstrated an association of a polymorphism in the DTNBP1 gene and psychosis among METH-dependent individuals (rs3213207;  $p=0.00025$ ). Furthermore, two haplotypes at these loci were also significantly associated with MAP ( $p$  values < 0.0015). Significant associations between schizophrenia and DTNBP1 also have been reported (Edwards et al. 2008; Straub et al. 2002). Consistent with this, reduced levels of dysbindin expression have been associated with the pathogenesis of schizophrenia (Talbot et al. 2004; Weickert et al. 2008) and thought to be related to glutamatergic neurotransmission. In schizophrenic patients, dysbindin-1 is reduced in intrinsic, glutamatergic terminals of the hippocampus which is inversely correlated with increased vesicular glutamate transporter (Talbot et al. 2004). As evidence is mounting that glutamate hypo-function may be related to the etiology

of schizophrenia (Konradi and Heckers 2003), it is postulated that DTNBP1 variants may contribute to MAP through pathways involving glutamatergic neurotransmission. Despite the many genetic studies of this gene, the link between functionality of these polymorphisms and dysbindin expression has not been investigated.

*Frizzled 3 (FZD3)* Frizzled proteins are cell surface receptors for secreted Wnt proteins (Wang et al. 2006a). Both frizzled and Wnt proteins are thought to be important in central nervous system (CNS) development. FZD3, the human Frizzled-3 gene, is widely expressed in the developing nervous system and is involved in axonal growth and guidance (Wang et al. 2006b). Wnt signaling plays a role in axonal remodeling and synaptic differentiation in the cerebellum (Cadet and Krasnova 2009; Lucas and Salinas 1997) and abnormal Wnt signaling has been linked to schizophrenia (Cotter et al. 1998). FZD3 maps to chromosome 8p21 and consists of eight exons. The 8p22-21 region has been identified as a susceptibility locus for schizophrenia in several studies (Blouin et al. 1998; Gurling et al. 2001; Pulver et al. 1995). However, genetic studies with the Frizzled-3 gene and schizophrenia have been contradictory, with both positive and negative associations among Han Chinese (Yang et al. 2003), Japanese (Zhang et al. 2004), and Korean (Jeong et al. 2006) populations. Interestingly, the association between Frizzled-3 and MAP has only been observed with haplotypes ( $p < 0.00002$ ) and not at the individual loci, which may indicate a required synergism between the polymorphisms for a phenotypic effect (Kishimoto et al. 2008b).

*Metabotropic glutamate receptor 2 (GRM2)* GRM2 is another gene involved in glutamatergic neurotransmission and found to be significantly associated with MAP (Tsunoka et al. 2010). GRM2 is located on chromosome 3p in a region linked to schizophrenia in several studies (Badner and Gershon 2002; Pulver et al. 1995). GRM2 encodes the group II metabotropic glutamate receptor 2 (mGlu2). mGlu2 is a G-protein coupled receptor involved in inhibition of adenylate cyclase and cAMP formation (Cartmell et al. 1999) and the major presynaptic group II autoreceptor activated by synaptically released glutamate (Kew et al. 2002). Although another group II metabotropic glutamate receptor, glutamate receptor 3 (mGlu3), has been implicated in etiological, pathophysiological and pharmacotherapeutic aspects of schizophrenia (Harrison et al. 2008; Lyon et al. 2008; Sartorius et al. 2008), no statistically significant association with GRM2 and schizophrenia was found in the Japanese population (Joo et al. 2001).

*5-Hydroxytryptamine (Serotonin) receptor 1A (5-HT1A)* 5-HT1A, the gene encoding the 5-HT receptor 1A, is a G

protein-coupled receptor which is widely expressed in the brain, including in the hypothalamus, hippocampus, and cortex. Through serotonin (5-HT) binding, this receptor mediates inhibitory neurotransmission. The serotonin system has been shown to be important in the neural processing of anxiety and the neurobiological control of learning and memory. Similar to the glutamatergic pathway, altered serotonergic neurotransmission is speculated to contribute to schizophrenia susceptibility. Evidence suggests that METH, which acts as a substrate for the 5-HT transporter, elevates extracellular 5-HT levels by both promoting the efflux via transporter-mediated exchange and by increasing cytoplasmic levels by disrupting storage of 5-HT in vesicles (Cadet and Krasnova 2009; Rothman and Baumann 2003). Although studies have explored whether there is an association between several of the genes involved in 5-HT regulation and MAP, only the rs878567 polymorphism in the 5-HT1A receptor was significantly associated using an alpha level of 0.001 as significant (Kishi et al. 2010). Polymorphisms in the 5-HT1A receptor have been associated with schizophrenia in several studies (Huang et al. 2004; Le Francois et al. 2008; Lemonde et al. 2003, 2004), including the rs878567 polymorphism. Currently, 5-HT(1A) receptor agonists are being considered for the treatment of schizophrenia (McCreary and Jones 2010).

*Prokineticin receptor 2 (PROKR2)* PROKR2 encodes prokineticin receptor 2 (PK-R2), an integral membrane G-protein coupled receptor for prokineticins. Prokineticins and their receptors are involved in a wide range of biological functions in multiple organ systems. In the CNS, prokineticin 2 modulates neurogenesis, circadian rhythms, and migration of the subventricular zone-derived neuronal progenitors (Cheng et al. 2002; Ng et al. 2005). The involvement of PK-R2 in circadian rhythm raises the question of whether this gene may be associated with mood disorders, a phenotype often observed in patients with drug addiction. Several animal studies have shown that METH increases expression of circadian genes in the brain (Iijima et al. 2002). The PROKR2 gene is located on chromosome 20p12.3, which was shown to be linked to bipolar disorder in three studies (Detera-Wadleigh et al. 1997; Fanous et al. 2008; Ross et al. 2008). An association between PROKR2 gene variants and major depressive disorder and bipolar disorder was reported in a Japanese population (Kishi et al. 2009b); however, this study was small and confirmatory studies will be necessary to validate this finding. Furthermore, these same investigators have shown that 3 individual SNPs in the PROKR2 gene (rs6085086, rs4815787, rs3746682), as well their haplotypes ( $p \leq 0.00019$ ), were associated with MAP (Kishi et al. 2010).

*Glycine transporter 1 (SLC6A9)* SLC6A9, which encodes the glycine transporter type 1 (GLYT1), is involved in glutamatergic neurotransmission, particularly at NMDA-type glutamate receptors. It is currently believed that termination of the different synaptic actions of glycine is produced by rapid re-uptake through two sodium- and chloride-coupled transporters, GLYT1 (located in the plasma membrane of glial cells) and GLYT2 (located in pre-synaptic terminals). GLYT1 regulates both glycinergic and glutamatergic neurotransmission by controlling the reuptake of glycine at synapses. The NMDA receptors are regulated in vivo by the amino acids glycine and D-serine. Glycine levels, in turn, are regulated by GLYT1, which serves to maintain low sub-saturating glycine levels in the vicinity of the NMDA receptors. Competitive antagonists of NMDA receptors produce a psychotic state in healthy subjects and exacerbate symptoms in schizophrenics. SLC6A9 has emerged as a key novel target for the treatment of schizophrenia. Morita et al. examined SLC6A9 among Japanese subjects with METH-dependence and psychosis (Morita et al. 2008). Two SNPs conferred an increased risk for MAP (rs2486001 and rs2248829) in addition to the haplotype T-G ( $p=0.000037$ ). It is speculated that variants of the SLC6A9 gene may affect susceptibility to MAP by modulating NMDA receptor function.

In summary, there is reasonably strong evidence that genetic variation in neurotransmitter systems and in neural development or growth is associated with risk for MAP. Of the seven genes with strong empirical support for association with MAP, four are involved in glutamatergic neurotransmission (DAOA, DTNBP1, GRM2 and SLC6A9). Potential epistatic (i.e. gene x gene) interactions among these glutamatergic genes should be investigated. Polymorphism in a key gene in serotonin system regulation and signaling (HTR1A) is also associated with risk for MAP, which suggests that other 5-HT system genes may also be good candidates. Finally, two genes with roles in CNS development (FZD3) and neurogenesis (PROKR2) may help to identify other genes as well as developmental processes that mediate vulnerability to MAP.

#### Gaps in genetic research

These studies reviewed in relation to MAP have examined candidate genes selected based on current concepts of neurobiology. Priorities for future genetic research on MAP include: replicate genetic associations within and across ethnically diverse populations; adjust for multiple comparisons to minimize false-positive associations; utilize linkage disequilibrium and tagSNP information to capture the polymorphic structure of candidate genes; increase statistical power by using larger population cohorts to minimize false-negative associations; improve phenotyping of MAP

by use of a continuum versus a categorical classification and account for trajectory of cessation, treatment response and relapse; identification of allele-specific *in vivo* activity in humans and non-human animals.

### METH neuropathobiology

Lines of evidence support the notion that METH abuse leads to neurodegeneration and, as such, may be a component part of MAP pathobiology (Krasnova and Cadet 2009). The neuropsychological events noted show deficits in attention, working memory, and decision making in METH addicts. Bioimaging and histopathologic evaluations show that the clinical findings parallel composite damage to dopamine and serotonin axons, loss of gray matter with linked hypertrophy of the white matter and microgliosis in different brain areas (Kuhn et al. 2008; Thomas et al. 2004a, b, 2008a, b; Xu et al. 2005). The molecular basis of such neurotoxicities, interestingly, parallel neural damage seen in a range of neurodegenerative disorders that include Alzheimer's and Parkinson's disease, HIV-associated neurocognitive disorders, and amyotrophic lateral sclerosis. Such neurotoxicity and inevitable neurodegeneration parallels the presence of oxidative stress, excitotoxicity, neuroinflammation, mitochondrial dysfunction, decreased antioxidants and stress patterns (Cadet and Krasnova 2009). These effects a host of intracellular organelle functions and suggests that a range of therapeutic strategies can be developed that would slow or reverse adverse neuronal events (Kosloski et al. 2010; Mosley and Gendelman 2010; Stone et al. 2009).

### Animal models

In this section, we review the published preclinical animal research that aims to simulate or directly understand some facet of METH-related psychosis. We will not attempt to survey the vast literature on neurobiologic and neurotoxic effects of METH exposure as it is beyond the scope and the focus of the present paper. The interested reader is referred to the following reviews on these topics (Cadet and Krasnova 2009; Fleckenstein et al. 2007; Volz et al. 2007). This section of the review, however, will have an eye toward the validity of the animal models that have been used to date, as well as identifying key gaps in the methods and research that need to be filled. Given the paucity of animal research directly focused on questions related to MAP, an important goal of this section is to make recommendations for future research that involves the development of translationally-relevant models that are reliable (i.e., reproducible) and predictive (Geyer and Markou 1995).

Clearly, establishing animal models that are predictive of the human phenomenon of interest (MAP in this case) will not happen without experimental situations and associated manipulations that are reproducible and consistent within and across laboratories. We agree with writers that espouse the best way to this broad form of predictive validity and to strong translational animal models is to work toward improving construct and etiological validity (Geyer and Markou 1995; Markou et al. 2009). For construct validity, attention to continually improving the match between what is measured at the behavioral (psychological) and neural levels in the animal models of MAP with what is believed to be the behavioral and neural processes underlying this psychosis in humans (Markou et al. 2009) is essential. As an example, if the current state of knowledge suggests that individuals with MAP have impaired sensorimotor gating that leads to sensory flooding and cognitive fragmentation, then some insight regarding the human condition may come from a better understanding of a similar attentional process in animal models. In this example, pre-pulse inhibition (PPI) may be of particular import. Pre-pulse inhibition refers to the decrease in startle response evoked by an auditory stimulus that is preceded by a pre-pulse stimulus (usually the startle stimulus at lower intensity and shorter duration). Deficits in PPI inhibition have been reported in patients diagnosed with schizophrenia, as well as in rats pretreated with METH (Abekawa et al. 2008) or have a history of self-administering METH (Hadamitzky et al. 2011; see later).

The strategy of searching for and establishing construct validity likely means that no single animal model will be sufficient to capture all processes relevant to the disorder of interest in humans. Also, this strategy is inherently translational. Working toward etiologic validity further encourages the communication and sharing of ideas, theories, and methods necessary for successful translational research (Markou et al. 2009). Etiologic validity refers to the matching of environmental and physiological precursors presumably responsible for the onset of the disorder. There is ongoing debate as to the extent that METH induces psychotic symptoms versus exacerbating pre-existing symptoms (see earlier). This is one of many unique instances in which animal models could serve to inform this important clinical issue. For instance, will rats intravenously self-administer enough METH to alter those behavioral and neural processes altered in humans diagnosed with MAP? Are the predisposing factors, whether environmental, neural, or genetic, thought to be relevant in human MAP contributing to such effects in the animal models? Prior research has demonstrated that under some conditions rats self-administering METH will show deficits in object recognition memory (Reichel et al. 2011) and PPI (Hadamitzky et al. 2011). Unfortunately, this research is

quite limited within the context of greater understanding of MAP in humans. Given that METH psychosis is associated with severe behavioral and neuropsychiatric complications (see earlier), there is a pressing need to definitively and precisely identify the behavioral and neurobiological mechanisms underlying the development of METH psychosis. As a result of this identification, behavioral interventions and psychopharmacological treatment strategies can then be developed.

Despite the limited work, animal studies have consistently shown that many psychological processes underlying clinical features of METH psychosis can be reproduced in a variety of animal species, including mice, rats, guinea pigs, cats and non-human primates (e.g., Japanese monkeys). Like METH addicts, animals that are chronically treated with a low (non-toxic) dose of METH gradually develop psychotic-like symptoms, such as a decrease in motor activity, an increase in stereotypies, decreased interest to external stimuli and surroundings, and decreased social functioning (Kuczenski et al. 2009). Also, some of the changed behavioral patterns (e.g., behavioral sensitization) persist even long after the cessation of drug treatment, and have a tendency to relapse or exacerbation upon re-exposure to the drug. Furthermore, concurrent antipsychotic drug treatment can prevent recurrence triggered by METH use (Misra et al. 2000). These results strongly suggests that animal models of METH psychosis have high face (e.g., similarities to clinical symptoms), construct (e.g., METH use and associated brain changes), and predictive validity (e.g., antipsychotic effect), and are effective in reproducing behavioral symptoms of human METH psychosis, mimicking the time course of symptom development, and its liability to exacerbation.

*Behavioral characteristics of MAP in nonhuman primates* Most of this work has been carried out by Japanese researchers since the early 1970s beginning during the decade immediately after World War II when METH abuse occurred in epidemic proportions in Japan (Ujike and Sato 2004). Japanese psychiatrists had observed an increased number of cases of MAP in chronic METH users and began to investigate the behavioral characteristics of the psychosis and associated biochemical mechanisms in animals. Nonhuman primate models are thought to be better than other species models in capturing complex and fine-grained behavioral abnormalities resembling human MAP, especially aspects of perceptual aberrations, social interaction, and interpersonal relationship. This is because monkeys, especially Japanese monkeys (*Macaca fuscata*) are well known to form a stable and intricate hierarchical society in which each member follows a certain rank order appropriate in interacting with others.

An early study provided a vivid description of acute and chronic effects of METH treatment on a group of Japanese

monkeys (Machiyama 1992). They gave monkeys intramuscular METH injection at 1.0 mg/kg from Monday to Saturday for 3–6 months. At the same time, physiological saline was given by intramuscular injection to the other animals that served as controls. Upon acute treatment, some monkeys showed motor excitation, whereas other showed motor suppression. They identified that this marked individual difference was due to the different behavioral traits of monkeys in the group. Active monkeys that showed enhanced repetitive motor activity to acute METH were those aggressive individuals occupying higher ranks while non-active monkeys, at the bottom in the ranking order, demonstrated a decrease in motor activity to acute METH treatment. Over the course of repeated drug treatment, some monkeys developed behavioral abnormalities in a variety of psychological domains. In the *sensorimotor* domain, after about 1 month treatment, some monkeys displayed a stereotypical body-fingering behavior which entailed continuous fingering and investigating certain parts of the body, such as the wrist, thigh, abdomen, penis, or scrotum (Machiyama 1992). In the *perception* domain, after about 2 months of repeated treatment, some monkey displayed hallucination-like perceptual distortions (e.g., “staring” at vacant space, floor or certain body parts of their own or cage mates, and at times touching with fingers). In the *social behavior* domain, some monkeys gradually lost interest in social interaction (e.g., grooming and mounting), and withdrew to stay in a location in the cage, and could suddenly show inexplicable aggression and fear, and broken behavioral response patterns (termed “splitting”). There were also marked individual differences. Monkeys, with middle and high ranks that responded actively to acute METH injection, demonstrated the most severe behavioral abnormalities in response to chronic METH treatment. Monkeys with lower ranks fared better and only exhibited mild changes. Two high ranked monkeys even died before the entire experiment was completed. After the termination of daily injections, some behavioral abnormalities disappeared, while others persisted for an extended period. In general, perceptual aberrations (e.g., staring, fixation) diminished rather rapidly and to a greater extent than deficits in sensorimotor (e.g., fixating) and social functioning (e.g., social withdrawal). Also, some monkeys who exhibited persistent behavioral changes that were easily identifiable by uninformed observers recovered better than others. Most interestingly, the psychotic behaviors of chronically treated monkeys could be re-triggered by a saline injection or a METH injection, mimicking clinical phenomena of stress and drug priming-induced relapse of METH psychosis.

One of the issues with these observational studies is the lack of formal assessments of psychological functions. Therefore, it is unclear what psychological function(s) (e.g.,

attention, working memory, episodic memory, executive functioning, emotional regulation, etc.) were impaired by chronic METH treatment that contributed to the observed behavioral abnormalities. The second issue is that the experimenter-controlled METH administration regimen did not mimic human METH use (via self-administration) and the constant dosing regimen used in the monkey studies also did not reflect the typical pattern of human METH use. Most METH abusers start with very low doses of the drug and have had a long history of progressively escalating their doses. Thus, human METH psychosis often appears during the course of escalating dosage of drug administration (i.e., “binges” or “runs”), and discontinuation of drug usage usually results in a rapid decline of the psychosis, closely paralleling urine drug levels (Angrist 1994; Davis and Schlemmer 1980; Kuczenski et al. 2009). This aspect of METH use pattern was not mimicked in these early studies.

There are several issues that may hinder the effort to delineate the neurobiological underpinnings of METH psychosis. The first is the lack of validated rodent behavioral models of METH psychosis. Unlike non-human primate models, which provide richer behavioral repertoires sensitive to the psychotomimetic effect of METH, most rodent studies focus on motor activity and stereotypy. Behavioral sensitization is taken as signs of METH psychosis (Martinez et al. 2005; Nestler 2001; Robinson and Becker 1986; Segal and Mandell 1974; Segal et al. 1981). One issue with psychomotor sensitization and stereotypy as behavioral indices of METH psychosis is that they do not seem to capture the emotional, cognitive, and perceptual disturbances that characterize human METH psychosis disorders. Other behavioral abnormalities induced by repeated METH treatment, such as disruption of PPI of acoustic startle response, may provide a better model (Braff et al. 2001). The following section discusses this rodent research in more detail.

*Behavioral characteristics of METH psychosis in mice and rats* To date, the behavioral models explicitly developed for studying symptoms of MAP in rodents fall into three broad categories: i) METH-induced deficits in PPI, ii) METH attenuation of social interactions, and iii) METH induced stereotypy and alterations in locomotion. The following narrative will provide an overview of this research and highlight some key findings that indicate their possible utility for understanding aspects of MAP in humans.

*Pre-pulse inhibition (PPI)* Rodents will startle to a sudden loud sound such as a 40 ms, 120-dB white noise. Under typical conditions, this startle reaction is reduced if this startle stimulus is preceded by a shorter and less intense pre-pulse stimulus (e.g., 20 ms, 72-dB white noise). This

inhibition of the startle is thought to measure sensorimotor gating (Braff and Geyer 1990). Individuals diagnosed with schizophrenia show deficits in PPI; an effect that can be simulated by acute and repeated treatment with METH. For example, Arai and colleagues found that mice pretreated with 3 mg/kg METH showed reduced PPI (Arai et al. 2008). A similar acute METH treatment protocol has been shown to be effective at producing PPI deficits in rats (Maehara et al. 2008). Of note, this deficit in PPI was not seen in mice treated acutely with 1 mg/kg METH (Arai et al. 2008). However, in that same report by Arai et al., repeated treatment with METH (1 mg/kg) for 7 days disrupted PPI and this deficit persisted after 7 days of abstinence from METH. More recently, Hadamitzky et al. (2011) report deficits in PPI in rats that had an extended history of self-administering intravenous METH. This research reflects an important advance in developing a translational model to study aspects of MAP. That is, like humans, this alteration in sensorimotor gating was self-induced by the rat.

Behavioral pharmacology research investigating the mechanism of the METH-induced deficits in PPI have focused either on the effects of established antipsychotic medications or on the effects of ligands thought to act on receptor processes involved in aspects of the psychosis. Along the former lines, the typical antipsychotic medication haloperidol has been shown to alleviate PPI deficits induced by acute treatment with METH (Maehara et al. 2008). Further, the atypical antipsychotics olanzapine and risperidone alleviated PPI deficits induced by repeated METH treatment (Abekawa et al. 2008). Arai and colleagues found that the GABA<sub>B</sub> agonist baclofen alleviated deficits in PPI induced by acute and chronic METH exposure (Arai et al. 2009). Further, the cholinergic system appears to be important for METH-induced deficits in PPI. For example, pretreatment with the muscarinic agonist oxotremorine blocked METH-induced deficits in PPI (Maehara et al. 2008). In this same report, the investigators did not find an effect of the nicotinic agonist nicotine. This result contrasts with (Mizoguchi et al. 2009) who found that pretreatment with nicotine alleviated PPI deficits produced by METH. Further, the nicotinic antagonist dihydro- $\beta$ -erythroidine (DH $\beta$ E) and METHyllycaconitine both blocked this ameliorative effect of nicotine indicating a role for  $\alpha$ 4 $\beta$ 2- and  $\alpha$ 7-containing nicotinic acetylcholine receptors. The most notable difference in protocol between these discrepant reports was that Maehara et al. 2008 used rats; whereas, Mizoguchi et al. 2009 used mice. Regardless, the comorbidity between METH and tobacco use, as well as schizophrenia and tobacco use, makes this an important area for future research.

*Social interaction* When a rat is paired with a conspecific, they show a variety of species-specific behaviors. These

behaviors include sniffing, grooming, crawling over or under, and nosing (Barnett 1963). Some researchers have suggested that alternations in social interaction resulting from METH exposure may be a useful model to study the paranoid and social anxiety symptoms of humans with MAP (Clemens et al. 2004; Rawson et al. 2002). Previous research has shown that acute METH treatment can alter social interaction. For example, Shinba et al. 1996 found that rats treated with either 0.1 or 1 mg/kg METH on average spent their time further away from the conspecific in the environment than saline controls [see also (Arakawa 1994)]. Perhaps of more interest from a modeling or simulation perspective is the more recent work by Clemens and colleagues showing ‘social withdrawal’ in rats following an abstinence period from METH (Clemens et al. 2007a, b). In one study, Clemens and colleagues administered METH at 2.5 or 5 mg/kg every 2 h for a total of 4 injections. METH increased general activity in the chamber across the entire 7.5 h treatment/measurement period regardless of dose (Clemens et al. 2004). Rats treated with the highest dose of METH (20 mg/kg total) also developed head weaving at the end of the treatment period, suggesting stereotypy with this protocol (see next section). Acute high dose METH increased activity and head-weaving. Albeit interesting, the most notable finding from the perspective of this report is that following 4 weeks of abstinence from METH these rats had significantly lower social interaction score than controls. Subsequently, this social withdrawal finding was extended to a treatment regimen in which rats were administered 8 mg/kg METH once per week for 16 weeks (Clemens et al. 2007a, b). In fact, the alterations in social interaction were seen after 7 weeks of abstinence.

*Stereotypy and alterations in locomotion* As the acute dose of METH increases, its behavioral effect in rats and mice generally shifts from inducing hyperactivity to inducing stereotypy. These effects of METH can become exaggerated (i.e., sensitization) with repeated treatment (Bevins and Peterson 2004; Kuczenski et al. 2009; Maehara et al. 2008; Ujike et al. 1989). Further, a handful of papers published in the 1960s showed that spontaneous wheel running, activity, and reactivity to external stimuli are blunted long after (e.g., 10 weeks) chronic treatment with METH has ceased [see Utena 1961, 1966; Yagi 1963; Yui et al. 2000 and Machiyama 1992 for more detailed discussion of this and related research]. The presentation of such behavioral alterations that sensitize with repeated treatment and persist with abstinence has been considered a model for some of the symptoms of psychosis (Machiyama 1992; Takigawa et al. 1993; Yui et al. 2000). Converging support for this notion comes from the overlap in the neurobiological processes underlying these motor effects of METH and that of psychosis in humans, as well as behavioral

pharmacologic work indicating the effectiveness of anti-psychotic medications. For instance, METH-induced locomotor stimulation is blocked by clozapine, haloperidol, and chlorpromazine (Maehara et al. 2008; Okuyama et al. 1997). Notably, METH-induced stereotypy in the work of Okuyama et al. 1997 was blocked by haloperidol and chlorpromazine, but not clozapine. Additional pharmacologic research has implicated the serotonergic, dopaminergic, and muscarinic systems in these effects (Balsara et al. 1979; Maehara et al. 2008; Ujike et al. 1989). For instance, Ujike et al. 1989 found that repeated daily METH treatment in rats (4 mg/kg for 14 days) increased locomotion and stereotypy. Pretreatment with dopamine D1 receptor antagonists SCH23390 or the D2 receptor antagonist YM-09151-2 blocked this sensitization.

Most of the repeated or chronic METH exposure research in this area involves a daily injection of METH for a prescribed number of days. Notably, a recent study by Kuczenski et al. (2009) sought to investigate these shifts in locomotor stimulation and stereotypy in rats, using an intravenous infusion protocol designed to more closely mimic the chronic escalating use of METH seen in humans and simulate the longer half-life of METH in humans (ca. 12 h in human versus 1 h in rats). Their findings confirm and extend earlier research describing the development of stereotypy, as well as disruption of sleep, in what seems to be a more translationally relevant model of MAP. Whether this is the case or not will need to await further research. However, one limitation of this model that will need to be overcome, if this model is to be more widely adopted, is the high mortality rate of the rats in the escalating METH exposure phase.

#### Neurobiological mechanisms underlying MAP

Chronic METH use profoundly changes the brain structures and chemistry (Chang et al. 2007). Studies on the METH-induced brain changes relevant to MAP have focused on the catecholaminergic systems (e.g., dopamine, norepinephrine, 5-HT, etc.). This approach makes sense given that METH is known to cause both acute and chronic neurotoxic changes in dopaminergic and serotonergic neurons in animals and humans and that psychosis in schizophrenia is thought to result from hyperactivity of the mesolimbic dopaminergic system. Some structural changes (enlarged lateral ventricle, enlarged basal ganglia, reduced hippocampal volume), that have been reported in patients with schizophrenia, have also been found in people who were chronic METH users, strongly indicating that these structural changes and their underlying mechanisms may be responsible for METH psychosis (Chang et al. 2007).

Human postmortem and imaging studies have consistently shown that chronic METH use causes a reduction of

dopamine transporter (DAT) density in the various dopaminergic systems, including the dorsal striatum, nucleus accumbens, and prefrontal cortex. However, this pronounced effect persists long after cessation of drug administration (Sekine et al. 2001, 2003; Volkow et al. 2001c; Wilson et al. 1996). The striatal dopamine D2 density is generally not affected. However, lower level of D2 receptor availability in the orbitofrontal cortex has been reported (Volkow et al. 2001a). Furthermore, there seem to be a significant negative correlation between the clinical severity of psychotic symptoms and DAT density, and a positive correlation between the duration of METH use and the severity of psychotic symptoms, suggesting that chronic METH use causes the reduction in DAT density, which may directly contribute to the development of METH psychosis (Iyo et al. 2004). Volkow et al. (2001b) also reported that the chronic METH-induced reduction in DAT is associated with motor and cognitive impairment. They found that there was a negative correlation between the DAT reductions and the impaired motor performance, and a positive correlation between the levels of DAT reductions and verbal memory performance: the lower the dopamine (DA) transporter level, the slower the motor responses, and the greater worsening of memory performance. However, because the reduced striatal DAT density tends to recover following METH abstinence (>6 months) (Volkow et al. 2001b) while METH psychosis persists long after the absence of METH use (Sato 1992), the direct and definite link between DAT reduction and METH psychosis is still lacking. It is possible that other permanent neuroadaptations caused by DAT reduction also play a role. Other human studies also reported that during the spontaneous recurrences of METH psychosis (referred to as “flashbacks”), there were increases in plasma DA and norepinephrine levels (Yui et al. 1999), consistent with the notion that increased DA neurotransmission, coupled with increased noradrenergic hyperactivity (due to stress) may contribute to psychotic symptoms.

In contrast to limited research on human subjects, there are many studies that have examined METH-induced brain changes in rodents. Although many structural and neurochemical changes induced by METH use/abuse has been revealed, whether those changes are directly related to MAP or even contributing to MAP is less certain. To ensure that the neurochemical changes discussed here are potentially relevant to the underpinnings of MAP, in this section, we will narrow our discussion to research that has demonstrated behavioral sensitization following human patterns of METH abuse (e.g., chronic and escalating dose regimens followed by repeated high-dose METH use). Behavioral sensitization refers to a progressive increase in motor and stereotypical responses to repeated drug treatment (Martinez et al. 2005; Nestler 2001; Robinson and

Becker 1986). Thus, the acute effect of METH use is not covered here. The rationale behind this approach is that endogenous sensitized dopaminergic function (e.g., progressively enhanced DA supersensitivity) is believed to be the critical cause of MAP (Ujike 2002; Ujike and Sato 2004). Because behavioral sensitization is the direct “readout” of central DA sensitization, it becomes an indispensable proxy measure of MAP. Because clinical observations suggest that MAP (as well as other psychostimulant psychosis) often emerges after repeated high-dose binges or runs, typically preceded by a more intermittent and escalating pattern of METH abuse, animal models that utilize a long-term intermittent and/or escalating dose regimen, followed by repeated high-dose METH runs are most likely to capture the clinical feature of MAP, and afford us the best chance to identify the neurochemical changes accompanied with MAP. Thus, studies utilizing this approach will be emphasized.

Chronic treatment of METH causes an increase of dopaminergic neurotransmission in the striatum. For example, Nishikawa et al. (1983) found that repeated METH treatment (6 mg/kg per day for 3–14 days) produced a robust behavioral sensitization in the form of augmented stereotypy. A later challenge injection of a lower METH dose (2 mg/kg) increased DA turnover (lower DA and higher 3, 4-dihydroxyphenylacetic acid levels, higher ratios of 3, 4-dihydroxyphenylacetic acid over DA) in the striatum and mesolimbic area of the sensitized animals. Kazahaya et al. (1989) also found that a challenge injection of METH after 7 days withdrawal from chronic administration of METH (4 mg/kg for 14 days) markedly increased DA release in the striatum. Segal and Kuczenski (1997) found that multiple short-interval METH injections (four daily injections at 2-hr intervals at 4.42 mg/kg) produced an augmented DA and serotonin release in both the nucleus accumbens and caudate-putamen in rats that were pretreated with METH for 16 days. These findings, coupled with the findings that repeated METH treatment directly sensitizes DA receptors in the nucleus accumbens and ventral tegmental area (Amano et al. 1996, 2003), and reduces striatal DAT (Izquierdo et al. 2010), strongly suggests that the enhanced striatal DA neurotransmission (e.g. increased DA release and supersensitivity of receptors) plays an important role in METH-induced behavioral sensitization. As discussed earlier, pharmacologic evidence is consistent with this finding. Ujike et al. 1989 showed that pretreatment of SCH 23390 (a selective D1 DA receptor antagonist) or YM-09151-2 (a selective D2 DA receptor antagonist) prevented the development of behavioral sensitization induced by repeated METH injection for 14 days and reduced the enhanced DA release produced by METH challenge.

Chronic METH users often take the drug continuously, and the plasma drug concentrations are elevated and

maintained throughout a 2–3 day binge. Studies simulating this pattern of human METH use often employ an escalating dose (ED)-multiple binge rodent model (Kuczenski et al. 2009; Segal and Kuczenski 1997, 1999). Kuczenski et al. (2009) developed a computer-controlled, intravenous drug delivery methodology with dynamic infusion which imposes a 12-hour half-life of the drug in rats to reproduce a plasma METH profile that approximates human METH pharmacokinetics. Using this drug administration procedure, they still found a prolonged elevation in caudate extracellular DA and behavioral sensitization.

In addition to DA, chronic METH use also produces changes in other neurotransmitter systems, which are also implicated in METH-induced behavioral sensitization. For example, it has been shown that repeated METH treatment (3 mg/kg/day for 30–50 days) increased serotonin levels in cats, which were restored by chlorpromazine treatment (Utena 1966). Rats receiving single daily injections of METH, followed by multiple runs (four daily injections at 2-hr intervals) showed a decrease in serotonin response in the striatum during runs (Segal and Kuczenski 1997). The findings that pretreatment with MDL 72222, a 5-HT<sub>3</sub> antagonist, can attenuate both the development and expression of METH-induced behavioral sensitization (Yoo et al. 2006), and repeated treatment with aripiprazole (a drug with 5-HT<sub>1A</sub> agonist action) during the withdrawal period from repeated METH treatment attenuated METH-induced behavioral sensitization (Futamura et al. 2010), also point to the notion that serotonin-mediated neurotransmission are related to the psychotomimetic effect of METH. Other neurotransmitters implicated in METH sensitization include substance P and sigma receptors, as evidenced by the findings that repeated METH treatment decreased the substance P receptor binding (Ujike et al. 1988) and sigma receptor antagonist BMY 14802 prevents the development of behavioral sensitization induced by repeated administration of METH (Ujike et al. 1992).

## Conclusion

There is great need for increased research to further understand factors related to MAP and how this psychosis affects METH use, dependence, and treatment outcomes. The current state of knowledge suggests that these factors, and their interaction, will span genetic to socioenvironmental influences. As such, research directed at the better understanding of MAP, by necessity, will need to be translational. This review identifies some gaps in our understanding and outlined potential future avenues of research that could help realize this goal of better treatment efficacy for METH-dependent individuals with MAP. For instance, there are no studies assessing protective factors

for MAP, which may mitigate against risk factors for psychosis. Does level of familial support, as an example, during treatment affect symptom expression and/or treatment outcome? Along these lines, there is a solid foundation of genetics work that has identified several candidate genes that may play a role in MAP development. However, larger studies of more ethnically diverse populations that likely have unique risk and protective factors are needed. Finally, advances in the development of animal models that show etiological and predictive validity are needed for a more complete understanding of the causes of MAP. These models would likely assist in drug development and behavioral interventions.

**Acknowledgements** This work was supported in part by the National Institutes of Health grant 1P01 DA028555-01

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