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ORIGINAL INVESTIGATION

Cognitive profile of ketamine-dependent patients compared with methamphetamine-dependent patients and healthy controls

Liang-Jen Wang[1,2] · Chih-Ken Chen[2,3] · Shih-Ku Lin[4,5] · Yi-Chih Chen[2,3] · Ke Xu[6] · Ming-Chyi Huang[4,5]

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Abstract

Background Ketamine has emerged as a major substance of abuse worldwide and has been listed with methamphetamine (METH) as two of the most widely available illicit substances in Taiwan. Only a few studies have examined the long-term consequences of chronic and heavy ketamine abuse. We compared the cognitive function of ketamine-dependent patients with that of METH-dependent patients and healthy controls.

Methods We recruited 165 participants (58 ketamine-dependent and 49 METH-dependent patients who sought treatment and 58 healthy controls) and evaluated them by using a cognitive test battery, the Brief Assessment of Cognition in Schizophrenia, with scores being estimated in reference to normative data in general population.

Results The ketamine-dependent patients had significantly poorer performance than did the controls in many cognitive tests, including verbal memory, motor speed, verbal fluency, and attention and processing speed, and the battery as a whole. METH-dependent patients exhibited poorer function in motor speed, verbal fluency, and attention and processing speed. The ketamine group performed poorer than did METH group in the domains of verbal memory, working memory, and attention and processing speed and the composite battery scores. A previous experience of ketamine-induced psychotomimetic symptoms, using higher doses of ketamine, and longer abstinence appeared to be associated with performance in some tests; however, the significance disappeared after multiple comparison correction.

Conclusions The ketamine-dependent patients had impaired cognitive function, and METH-dependent patients exhibited intermediate performance between ketamine-dependent patients and healthy controls. Given the growing population of ketamine abusers, public education on the cognitive consequences should be provided.

Keywords Ketamine · Methamphetamine · Substance dependence · Cognition · Psychosis

Introduction

Ketamine, a derivative of phencyclidine, was marketed as a short-acting general anesthetic for human and veterinary use in the 1990s. In the past two decades, ketamine has emerged as a major substance of abuse in many parts of the world (Dillon et al. 2003; Kalsi et al. 2011; Morgan et al. 2012), including Europe and Asia (Chevallier et al. 2015; Gozzi et al. 2011; Joe Laidler 2005). The lifetime prevalence of ketamine abuse in the club scene ranges from 6.7 to 67.8% across countries (Kalsi et al. 2011). In Taiwan, ketamine has become a major illicit drug next to heroin and methamphetamine (METH) and the primary new psychoactive substance over the past decade (Feng et al. 2016), particularly among school-attending adolescents (Chen et al. 2009). Given the rising prevalence of ketamine abuse, there is an urgent need to establish the consequences of the long-term use of this drug.

Dr Chih-Ken Chen as the co-first author for equivalent contribution to the article.

✉ Ming-Chyi Huang
mch@tpech.gov.tw

1 Department of Child and Adolescent Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

2 Department of Psychiatry, Chang Gung Memorial Hospital, Keelung, Taiwan

3 Chang Gung University School of Medicine, Taoyuan, Taiwan

4 Taipei City Psychiatric Center, Taipei City Hospital, Taipei, Taiwan

5 Department of Psychiatry, School of Medicine, College of Medicine, Taipei Medical University, 309, Song-De Road, Taipei, Taiwan

6 Department of Psychiatry, Yale School of Medicine, New Heaven, CT, USA

Cognitive impairment is one of the multiple adverse outcomes associated with ketamine abuse (Bokor and Anderson 2014; Morgan et al. 2012; Morgan et al. 2010). The pharmacological effect of ketamine through the blockade of N-methyl-D-aspartate (NMDA) glutamate receptors, which is central to mechanisms underlying learning and memory, may account for the disruption of cognition (Morgan et al. 2012). Moreover, the effects of ketamine on other neurotransmitter systems may play a role (e.g., inhibition of muscarinic acetylcholine receptor function (Durieux 1995) and induction of dopamine release (Rabiner 2007)). A 1-year longitudinal study found that increasing ketamine use was correlated with decreasing cognitive performance (Morgan et al. 2010). Active ketamine users (i.e., those who use ketamine 1–4 times per week and had the last dose within the past month) exhibited deficits over an array of cognitive tests (Morgan et al. 2010; Tang et al. 2013), and the deficits appeared to be persistent (Morgan et al. 2010). Studies that employed magnetic resonance imaging to examine treatment-seeking ketamine-dependent patients abstaining from ketamine for at least 2 days have demonstrated that multiple brain areas were affected—including the frontal, parietal, occipital, and limbic lobes; brainstem; and corpus striatum—and that the sites of atrophy became more prominent with an increased duration of ketamine abuse (Liao et al. 2011; Wang et al. 2013). In addition, the reduction in the frontal gray matter volume was dose dependently correlated with the duration and cumulative dose of ketamine use (Liao et al. 2011). One animal study showed that brain functions were impaired in monkeys treated with ketamine for 6 months; however, such changes were not found after ketamine treatment for only 1 month (Sun et al. 2014). These observations collectively suggest that chronic and heavy administration of ketamine might predispose individuals to more serious cognitive impairment.

METH, one of the most toxic drugs of abuse associated with significant public health problems worldwide, has also been associated with various neuropsychiatric toxicities through its potent sympathomimetic effects (Dean et al. 2013; Panenka et al. 2013). The ensuing complex neurochemical abnormalities in the brain, for example dopamine system dysfunction, potentially contribute to METH-related emotional disturbances, impulsivity, and cognitive deficits (London 2016; London et al. 2015; Okita et al. 2016). A meta-analysis of 17 cross-sectional studies found that participants with METH abuse or dependence exhibited impairment in the majority of cognitive domains (Scott et al. 2007). One recent report systemically reviewing the existing literature indicated that although a unanimous consensus for METH-induced cognitive decline is still lacking, METH abuse is associated with at least mild cognitive deficits in some users (Dean et al. 2013). Noteworthily, it has been highlighted previously that when examining differences in cognitive performance between METH and other groups, a normative dataset should be considered as a reference to compare performance against appropriate normative scores (Hart et al. 2012).

We previously found that METH abusers with a prior history of ketamine use had poorer cognitive performance than did those without a prior history of ketamine use (Chen et al., 2015a, b). However, we could not distinguish the effect of ketamine use from that of METH use on cognitive function and did not use a control group. Given the prevalent problems associated with the use of ketamine and METH in our society, additional information regarding their long-term adverse effects with repeated dosing is required for public education (Huang et al. 2016). Because structural changes in the brain associated with chronic and heavy ketamine abuse involve multiple regions and may be more diffuse than with METH abuse (Wang et al. 2013), we hypothesized that ketamine-dependent patients would have poorer cognitive function than METH-dependent patients. We first determined the performance of a clinical sample of recently abstinent ketamine-/METH-dependent patients over a range of cognitive functions by using a healthy control group for comparison, with reference to normative data in our population (Wang et al. 2017). Second, we examined the relationship between cognitive function and ketamine/METH use variables and whether a prior experience of drug-induced psychotomimetic symptoms affects cognitive outcomes.

Methods

Study participants

We conducted a cross-sectional, case–control study from September 2013 to December 2015 by recruiting treatment-seeking patients consecutively at two study sites: Department of Addiction Sciences, Taipei City Psychiatric Centre, Taipei City Hospital, and Department of Psychiatry, Chang Gung Memorial Hospital. To minimize the impact from acute intoxication, only patients had discontinued their drug of abuse for at least 24 h were invited to participated in this study. Both sites provide outpatient and inpatient services for individuals with substance use disorders and conduct various treatment programs, such as individual psychotherapy, group psychotherapy, family counseling, and vocational training, to help patients manage withdrawal symptoms, prevent relapse, and maintain abstinence. The study protocol was in accordance with Declaration of Helsinki and approved by the Institutional Review Boards of both the sites (No: TCHIRB-1020220 and 103-6849C).

Ketamine group

Fifty-eight ketamine-dependent patients participated in the study after an improvement in their withdrawal symptoms,

such as anxiety, shaking, sweating, palpitations, and sleep impairment, as has been suggested previously (Critchlow 2006; Morgan et al. 2012). The inclusion criteria were as follows: (a) age between 18 and 60 years; (b) fulfilling DSM-IV-TR criteria for ketamine dependence, as verified by two board-certified psychiatrists; (c) no other substance use disorder (including abuse and dependence) in the past year, except nicotine; (d) no history of major psychiatric disorders (including schizophrenia, bipolar disorder, and major depressive disorder with psychotic features) or antipsychotic treatment; (e) no known systemic or neurological diseases that would affect cognitive performance; and (f) ability to read Chinese and provide informed consent.

METH group

We recruited 49 treatment-seeking METH-dependent patients who did not exhibit active withdrawal symptoms based on DSM-IV-TR diagnostic criteria for amphetamine withdrawal. The inclusion criteria were as follows: (a) age between 18 and 60 years; (b) fulfilling DSM-IV-TR criteria for METH dependence, as verified by two board-certified psychiatrists; (c) no other substance use disorder (including abuse and dependence) in the past year, except nicotine; (d) no history of major psychiatric disorders or of antipsychotic treatment; (e) no known systemic or neurological diseases that would affect cognitive performance; and (f) ability to read Chinese and provide informed consent.

Control group

The control group consisted of 58 healthy individuals recruited from Kaohsiung Chang Gung Memorial Hospital staff and from community volunteers in Kaohsiung City. The recruitment criteria were as follows: (a) age between 18 and 60 years; (b) no history of ketamine, METH, or other illicit drug use; (c) no history of major psychiatric disorders (including schizophrenia, bipolar disorder, major depressive disorder with psychotic features, and organic mental disorders); (d) no known systemic or neurological diseases that would affect cognitive performance; and (e) ability to read Chinese and provide informed consent.

Clinical assessment

After providing informed consent, participants were interviewed face-to-face by WLJ, CKC, and MCH by using the Chinese version of the Diagnostic Interview for Genetic Studies (Chen et al. 1998) to confirm the diagnosis of ketamine/METH dependence and collect information regarding their sociodemographic characteristics and ketamine/METH use patterns (e.g., age at first use, average dosage of METH/ketamine, and duration of abstinence since the last ketamine/METH use). Ketamine users might manifest psychotomimetic symptoms that are similar to the prodromal symptomatology of schizophrenia (Morgan et al. 2010), typically with dissociation, schizotypy, and subclinical delusions (Morgan et al. 2012). METH users might present with delusions and hallucinations (Glasner-Edwards and Mooney 2014). Therefore, we recorded a positive history of ketamine-induced psychotomimetic or dissociative symptoms for the ketamine group and of METH-induced psychotic symptoms for the METH group.

Cognitive assessment

The cognitive functions of all participants were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al. 2004). The BACS test battery was initially designed to measure multiple domains of cognitive functions that are strongly correlated with those of real-world functioning in patients with schizophrenia (Keefe et al. 2006). Further research supported its utility in assessing cognitive deficits in individuals with psychotic disorders or healthy controls (Hochberger et al. 2016). The BACS is also a practical cognitive assessment tool for METH, ketamine (Chen et al. 2015a; Chen et al. 2015b; Yamamuro et al. 2015), or cannabis users (Hanna et al. 2016). The validity of the Chinese version of BACS has been proven to be satisfactory (Wang et al. 2016) and can be easily administered, requires approximately 30 min, generates a high completion rate in patients, and has high test-retest reliability. The battery includes the List Learning Test, Digit Sequencing Task, Token Motor Task, Category Instances Test, Controlled Oral Word Association Test, Symbol Coding, and Tower of London test, which assessed verbal memory, working memory, motor speed, verbal fluency, attention and processing speed, and executive function, respectively.

The primary measure of each BACS domain was standardized by calculating T or Z scores. Finally, a composite score was calculated by comparing each patient's performance on each measure with the performance of the normal population and was the T or Z score of that sum (Keefe et al. 2008). A T score of 50 for each scale indicates average functioning with reference to the normal population of the same age and sex, and every 10 points represent one standard deviation. The T scores for each scale in this study were calculated on the basis of normative data in Taiwan (Wang et al. 2017).

Statistical analyses

Data were analyzed using the statistical software package SPSS (Version 21.0; SPSS Inc., Chicago, IL, USA). Variables are represented as either mean (± standard deviation) or frequency (%). A two-tailed $P < 0.05$ was considered statistically significant.

An intergroup comparison of categorical and continuous variables was performed using the chi-square test and the one-way analysis of variance or *t* test, respectively. Intergroup differences in BACS performance were determined using a general linear model with LSD post hoc tests, after controlling for age, sex, and the education level. Additionally, a general linear model was employed to evaluate the effects of ketamine/METH use patterns on each BACS domain in respective users. The *T* scores from the aforementioned six domains and the composite BACS score were set as dependent variables. Bonferroni correction by considering $P < 0.0071$ (= 0.05/7) was used for multiple testing in seven linear models.

Results

Participant characteristics

Table 1 lists the characteristics of the 58 ketamine users, 49 METH users, and 58 healthy controls. The participants in the METH group were older than those in the ketamine group; however, the distribution of age or sex did not differ between the METH and control groups or between the ketamine and control groups. The control participants had the highest education level, followed by ketamine and METH users. The ketamine group had a shorter drug administration duration (8.6 ± 4.1 vs. 14.7 ± 7.6 years, $P < 0.001$) and abstinence period (7.7 ± 6.4 vs. 27.0 ± 26.0 days, $P < 0.001$) than did the METH group. Furthermore, 86.2% of the ketamine users had a history of ketamine-induced psychotomimetic or dissociative symptoms, whereas 65.3% of the METH users had a past experience of METH-induced psychotic symptoms.

Cognitive function between groups

Table 2 shows the performance (*T* score) of the ketamine users, METH users, and healthy controls in each BACS domain after adjustment for age, sex, and the education level. Significant differences were found across the three groups in the five BACS domains, namely verbal memory, working memory, motor speed, verbal fluency, and attention and processing speed, as well as the composite BACS score. No significant difference was observed in executive function among the three groups.

Post hoc test results revealed that the ketamine users exhibited poorer performance in verbal memory, motor speed, verbal fluency, and attention and processing speed, as well as a lower composite BACS score, than did the controls. In addition, the ketamine users exhibited lower verbal memory, working memory, and attention and processing speed than did the METH users (Table 2). The METH users exhibited

Table 1 Characteristics of ketamine-dependent patients, methamphetamine (METH)-dependent patients, and healthy controls

	Ketamine patients ($n = 58$)	METH patients ($n = 49$)	Controls ($n = 58$)	Statistics value
Age (years)	31.1 ± 6.9	35.9 ± 8.9	33.1 ± 7.6	$F = 5.013$[a], df = 2, $P = .008$**
Sex				$\chi^2 = 0.941$, df = 2, $P = .625$
Men	43 (74.1)	40 (81.6)	46 (79.3)	
Women	15 (25.9)	9 (18.4)	12 (20.7)	
Married				$\chi^2 = 12.033$, df = 2, $P = .002$**
Married	7 (12.1)	11 (22.4)	23 (39.7)	
Single	51 (87.9)	38 (77.6)	35 (60.3)	
Years of education	12.2 ± 2.6	9.8 ± 2.0	15.9 ± 1.9	$F = 105.750$[b], df = 2, $P < .001$***
Age at first ketamine/METH use (years)	22.5 ± 6.9	21.2 ± 6.4	–	$t = 1.044$, df = 105, $P = .299$
Duration of ketamine/METH use (years)	8.6 ± 4.1	14.7 ± 7.6	–	$t = 5.002$, df = 105, $P < .001$***
Duration of abstinence (days)	7.7 ± 6.4	27.0 ± 26.0	–	$t = 5.072$, df = 105, $P < .001$***
Average dose of ketamine use (g/day)/METH use (g/week)	6.8 ± 5.7	3.9 ± 4.3	–	N/A
Experience of psychotic symptoms induced by drug[c]	50 (86.2)	32 (65.3)	–	$\chi^2 = 6.480$, df = 105, $P = .011$*

Note: data are expressed as mean ± SD or *n* (%)

df, degree of freedom; Abbreviation in post-hoc test: *K*, ketamine users; *M*, METH users; *C*, controls; *N/A*, not applicable

*$P < .05$, **$P < .01$, ***$P < .001$

[a] M > K**

[b] C > K***, C > M***, K > M***

[c] A past experience of ketamine-induced psychotomimetic or dissociative symptoms in the ketamine group or METH-induced psychotic symptoms in the METH group

Table 2 Neurocognitive performance of ketamine-dependent patients, methamphetamine (METH)-dependent patients, and healthy controls

	Ketamine users ($n = 58$)	METH users ($n = 49$)	Controls ($n = 58$)	Statistics (F value)	P value	Post-hoc test
Verbal memory	38.5 ± 13.0	40.2 ± 10.4	49.2 ± 11.3	4.300	.015*	K < M*, K < C*, M ≈ C
Working memory	42.8 ± 11.3	46.7 ± 13.4	49.0 ± 10.6	4.159	.017*	K < M**, K ≈ C, M > C*
Motor speed	40.0 ± 16.0	41.4 ± 13.1	49.7 ± 9.8	6.754	.002**	K ≈ M, K < C***, M < C*
Verbal fluency	39.8 ± 9.6	38.4 ± 7.5	48.4 ± 10.1	4.134	.018*	K ≈ M, K < C**, M < C*
Attention and processing speed	32.3 ± 12.9	36.0 ± 12.2	51.2 ± 11.2	19.387	<.001***	K < M*, K < C***, M < C**
Executive function	47.7 ± 10.9	46.0 ± 15.0	50.9 ± 9.2	0.271	.763	K ≈ M ≈ C
Composite score	32.0 ± 15.1	33.1 ± 16.2	49.4 ± 11.2	8.003	<.001***	K ≈ M, K < C***, M ≈ C

Note: data are expressed as T scores (mean ± SD) of each domain of the Brief Assessment of Cognition in Schizophrenia (BACS); Statistical values were determined using the General Linear Model with LSD post hoc tests, controlling for age, gender and education levels. Degree of freedom (df) 1 (between groups) = 2; df2 (within groups) = 159

Abbreviation in post hoc test: *K*, ketamine users; *M*, METH users; *C*, controls

*$P < .05$; **$P < .01$; ***$P < .001$

poorer motor speed, verbal fluency, and attention and processing speed than did the healthy controls, but not other cognitive domains or battery as a whole.

Ketamine/METH use variables and cognitive function

The effects of ketamine use patterns on each BACS domain were analyzed in the 58 ketamine users (Table 3). After adjustment for age, sex, and the education level, the average dose of ketamine use was found to be negatively correlated with verbal fluency. The duration of ketamine abstinence was positively correlated with verbal memory and verbal fluency. The ketamine users with a previous experience of psychotomimetic symptoms had poorer verbal fluency and attention and processing speed than did those without the symptoms. However, after adjusting for multiple testing, none of the ketamine use variables was correlated with cognitive performance.

Table 4 presents the relationship between METH use patterns and cognitive function in the 49 METH users. After adjustment for age, sex, and the education level, no characteristics of METH use were found to be significantly associated with the performance in other BACS subtests.

Discussion

In the present study, after adjusting for age, sex, and the education level, we found that the treatment-seeking ketamine-dependent patients exhibited significantly poorer performance

Table 3 Relationships of ketamine using patterns and each BACS domain among ketamine-dependent patients ($N = 58$), controlling for age, gender, and level of education

	Verbal memory		Working memory		Motor speed		Verbal fluency		Attention and processing speed		Executive function		Composite score	
	B	P value	B	P value	B	P value	B	P value	B	P value	B	P value	B	P value
Sex (male vs. female)	2.721	.483	3.814	.243	.074	.988	3.364	.217	9.918	.009**	.249	.942	4.549	.319
Age	−.017	.948	.059	.788	−.666	.046*	−.088	.630	.279	.261	.107	.646	.010	.975
Years of education	1.338	.051	1.739	*.003***	.315	.708	.641	.177	.586	.358	−.072	.904	1.372	.087
Duration of ketamine use	−.400	.365	.055	.881	−.206	.709	−.564	.071	−.315	.449	.188	.631	−.291	.574
Dose of ketamine use	−.190	.540	−.293	.263	.177	.649	−.539	.016*	.013	.964	.357	.199	−.044	.905
Duration of abstinence	.706	.015*	−.003	.991	.217	.539	.403	.045*	.180	.499	−.212	.399	.392	.240
Experience of psychotomimetic symptoms[a]	−4.941	.322	−1.052	.801	−9.667	.124	−7.649	.031*	−11.599	.016*	−4.433	.318	−11.496	.053

Note: Data are expressed as statistical values using the general linear model

*$P < .05$; **$P < 0.0071$ (= 0.05/7) in italics after adjustment for multiple testing of the seven linear regression models

[a] A past experience of ketamine-induced psychotomimetic or dissociated symptoms

Table 4 Relationships of methamphetamine (METH) using patterns and each BACS domain among METH-dependent patients ($N = 49$), controlling for age, gender, and level of education

	Verbal memory		Working memory		Motor speed		Verbal fluency		Attention and processing speed		Executive function		Composite score	
	B	*P* value	B	*P* value	B	*P* value	B	*P* value	B	*P* value	B	*P* value	B	*P* value
Sex (male vs. female)	− 1.451	.731	3.761	.480	− 1.570	.777	1.972	.529	1.010	.841	− 4.511	.461	− 1.506	.824
Age	.108	.696	.652	.067	.174	.632	− .232	.262	− .343	.303	− .183	.648	− .058	.896
Years of education	1.483	.064	.326	.742	− .886	.391	.764	.194	.722	.442	1.477	.197	1.328	.295
Duration of METH use	− .344	.266	− .308	.427	.162	.688	.326	.158	.432	.242	− .125	.778	.147	.765
Average dose of METH use	.252	.486	.160	.724	− .079	.867	− .092	.732	− .090	.834	− .163	.754	− .088	.878
Duration of abstinence	− .041	.516	− .043	.587	.013	.874	.016	.736	.102	.175	.058	.521	.035	.728
Experience of psychotic symptoms[a]	− 2.188	.525	− 4.363	.316	− 1.905	.673	− 1.891	.459	− 5.538	.181	− 7.233	.151	− 8.605	.124

Note: Data are expressed as statistical values using the general linear model. Statistical significance was set as $P < 0.0071$ (= 0.05/7) after adjustment for multiple testing of the seven linear regression models

[a] A past experience of METH-induced psychotic symptoms

than did the controls in many cognitive tasks, namely verbal memory, motor speed, verbal fluency, and attention and processing speed, as well as in the cognitive battery as a whole. The METH users exhibited poorer performance than did the controls in motor speed, verbal fluency, and attention and processing speed, but not in other cognitive tests or composite battery scores. To the best of our knowledge, this is the first study to indicate that the ketamine-dependent patients performed poorer than the METH-dependent patients. In addition, although a past history of ketamine-induced psychotomimetic symptoms and higher doses of ketamine use appeared to be associated with poorer performance in some cognitive tests, whereas a longer duration of abstinence was found to be associated with better cognitive performance, the significance of these associations was not observed after multiple testing.

Our results support the existing evidence that indicates a link between ketamine abuse and cognitive impairment. Similar to the findings of previous studies, the ketamine-dependent patients enrolled in the present study showed impairment in the domains of verbal memory, attention and processing speed, verbal fluency (Chan et al. 2013; Morgan et al. 2004a; Morgan et al. 2009, 2010), and mental and motor speed (Tang et al. 2013), but not in working memory or executive function. The spared dysfunction in working memory or executive function might indicate a compensatory psychological adaptation by ketamine users to manage other impairments (Morgan et al. 2004b). In addition, a 1-year longitudinal study found that frequent ketamine users exhibited persistent decrements in multiple domains of cognitive tests, but the performance in the Stockings of Cambridge task, which is a test based on the Tower of London test that was adopted in this study to evaluate executive function, was comparable to that of controls (Morgan et al. 2010). Moreover, consistent with the observation from animal studies suggesting that ketamine-induced neurotoxicity is reversible (Jevtovic-Todorovic et al. 2001), we found that a longer period of ketamine abstinence was associated with an improved function in some cognitive tests (verbal fluency and verbal memory); thus, cognitive deficits might be reversible along with prolonged abstinence. Collectively, these observations suggest that chronic and heavy ketamine use has profound effects on most cognitive functions. However, whether the cognitive deficits would persist or be reversible following a longer period of abstinence should be addressed in future studies.

The ketamine group showed poorer performance than did the METH group in verbal memory, working memory, and attention and processing speed, despite the ketamine users having a shorter duration of drug use. Further extracting the patients who had discontinued their drug of abuse for at least 3 days resulted in 44 (out of 58) ketamine-dependent and 40 (out of 49) methamphetamine-dependent patients; among these patients, the ketamine group still exhibited poorer performance in working memory and attention and processing speed than did the METH group; however, verbal fluency and verbal memory function were comparable between the groups (data not shown). This finding is consistent with the aforementioned statement that verbal function in the ketamine group might improve with a longer abstinence. However, the reasons underlying the observation that the ketamine group exhibited poorer cognitive function than did the METH group are not clear. NMDA receptors are widely distributed in both cortex and subcortical systems. Chronic ketamine exposure suppresses the NMDA-mediated drive on GABA

interneurons, thus disinhibiting glutamate release. The ensuing widespread glutamate-mediated excitotoxicity and disorganized cortical activity in turn cause disruption in cognitive function (Moghaddam and Krystal 2012). In line with our observations, imaging studies have found that ketamine abuse exerts a diffuse effect on the brain, affecting both the gray and white matter (Wang et al. 2013; Yu et al. 2012). Despite evidence showing a reduction in global cortical gray matter thickness in METH abusers (Okita et al. 2017), we speculate that ketamine-induced neurochemical perturbation in NMDA receptors is nonselective and ubiquitous, involving multiple systems, and thus causes more cognitive impairments compared with METH abuse.

METH can produce significant and persistent neurophysiological changes through the potent sympathomimetic action, thereby affecting cognitive function (Panenka et al. 2013). Despite mixed results, METH abuse is overall considered to be associated with cognitive decline, and the decline is likely to be mild in early-to-middle adulthood and mediated by factors such as age and genetic variability (Dean et al. 2013). A longitudinal study found that cognitive deficits might have only occurred in a certain subset of METH abusers (Iudicello et al. 2010). In addition, not all aspects of cognition are equally affected by chronic METH use (Dean et al. 2013). Our METH patients, with an age distribution similar to that in most of the relevant reports (mean age in the 30s), exhibited impaired performance only in some tests (motor speed and attention and processing speed); however, the functioning in other cognitive domains and even the cognitive battery as a whole was comparable to that of the controls. One prior study also showed that current METH users (i.e., METH use within the prior 72 h) exhibited deficits only in memory and information manipulation and that their scores in other measures were within normal ranges (Simon et al. 2000). The varied outcomes in different domains of cognition have also been shown in studies including abstinent METH-dependent individuals who had discontinued METH for various durations: 5–14 days (Kalechstein et al. 2003), 1 month (Simon et al. 2010), 3 months (Johanson et al. 2006), or 6 months (Zhong et al. 2016). The differential distribution of monoamines that is affected by METH in the brain has been suggested to account for the varied impact of METH on the broad range of cognitive domains (Panenka et al. 2013).

The present study showed a nonsignificant trend that ketamine use variables and psychotomimetic experiences might affect the performance in cognitive tests. Specifically, the dose of ketamine use negatively affected verbal fluency, whereas the duration of abstinence was positively associated with verbal memory and verbal fluency. Consistent with our observation, repeated ketamine use was reported to cause functional impairment mainly along the verbal axis (Tang et al. 2013), and heavier lifetime ketamine use was correlated to verbal learning and verbal memory deficits (Chan et al. 2013). The dose dependence of cognitive decline has also been noted in an imaging study that showed ketamine-associated reduction in gray matter volume increased with the cumulative dose of ketamine use (Liao et al. 2011). Regarding the association of psychotomimetic symptoms with cognitive impairment, some evidence suggests that ketamine has similar affinity at NMDA and dopamine D2 receptors (Kapur and Seeman 2002), both of which reciprocally interact with and modify the function of each other (Wang et al. 2012). The enhanced dopaminergic activity and D2 agonistic property might explain the psychotomimetic action of ketamine (Rabiner 2007; Wang et al. 2012). Thus, the interplay of the neurochemical perturbation between dopamine and NMDA receptor systems could be relevant to the association between psychotic symptoms and cognitive impairment. Nevertheless, future studies will be required to examine whether these near-significant correlations hold in a larger sample.

Although using a normative dataset as a reference to estimate the standardized scores to compare cognitive functions between groups was a strength of this study, it had some limitations. First, we did not have data of the premorbid intellectual function of the three groups, and the age and education levels were not equivalent between the groups. Second, some variables not examined in our study, such as lifestyle habits, alcohol drinking, and comorbid disorders, might contribute to complexities in ascribing our observations as the consequences of drug use. Although we had excluded patients with other substance abuse in the past year and those with schizophrenia, bipolar disorder, or major depressive disorder with psychotic features, the confounding effect from preexisting drug abuse and another psychiatric comorbidity may still exist. Third, cigarette smoking can affect the results of cognitive tests (Domier et al. 2007; Mendrek et al. 2006), but the smoking information was not available in our study. Fourth, using only a single test to measure a particular cognitive domain may not reflect the true functional relevance, which should be assessed using multiple tasks (Dean et al. 2013). Fifth, to reduce the influence of withdrawal on performance, the cognitive assessment was performed after the withdrawal symptoms had subsided. However, we evaluated patients' withdrawal based on clinical observations instead of a reliable tool to measure the severity. Therefore, subclinical withdrawal symptoms may have affected assessment results. In addition, the withdrawal duration not only varies interindividually but also depends on the characteristics of the drug of abuse. Because ketamine and METH possess rather distinctive pharmacological profiles—for example, the duration of drug effect is 30–45 min and ≥ 8 h, whereas the elimination half-life is 2–3 h and 11–13 h, respectively, for ketamine and METH, respectively (Cruickshank and Dyer 2009; Domino 2010)—the length of withdrawal duration may thus differ significantly between groups (7.7 ± 6.4 and 27 ± 26 days for ketamine and METH groups, respectively, $P < 0.001$; Table 1); this

may limit the comparability between the groups and only reflect a general profile of cognitive discrepancy. Finally, we assessed cognition in individuals with a verified diagnosis of drug dependence and who had been in initial abstinence. The results could not be generalized to those who still actively use ketamine/METH or in whom the severity of drug use had not achieved the level of dependence.

Conclusion

This study demonstrated that treatment-seeking ketamine-dependent patients were impaired in most of the cognitive tests and had poorer performance than did METH-dependent patients who exhibited deficits only in some of the cognitive tests. Because we assessed cognitive function in patients only during early stage abstinence, future studies are stipulated to investigate alterations in cognitive ability following a longer term of abstinence in ketamine or METH abusers. Given the growing population of recreational users, advice on the deleterious consequences of ketamine or METH dependence on cognitive functions should be provided.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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