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A multicenter cross-sectional study of gambling disorder among patients with methamphetamine use disorder in drug rehabilitation centers: prevalence, correlates, and network analysis

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Abstract

Background This study sought to investigate the prevalence, correlates, and network structure of the manifested symptoms in gambling disorder (GD) among methamphetamine (MA) use disorder (MUD) patients in China.

Methods We interviewed 1069 patients using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA), Chinese version. Besides MA and other substance use disorders, GD was also ascertained by SSADDA. Other psychiatric diagnoses were ascertained, including major depressive episodes (MDEs), antisocial personality disorder, suicide and self-harm, and environmental factors, including childhood experiences.

Results Of 1069 participants, 711 met the DSM-5 diagnostic criteria for MUD. Among the 711 participants with MUD, 52.3% met DSM-5 diagnostic criteria for GD. We found that alcohol use together with MA, childhood violent experiences, MDEs, severe MUD, and gambling duration significantly differed between MUD participants with and without GD. In the GD-MUD network, the central symptoms were gambling preoccupation (GD1), giving up important activities (MUD6), financial trouble (GD9), and MA tolerance (MUD5). MA tolerance (MUD5) also served as a bridge symptom across the network, exhibiting substantial associations with gambling preoccupation (GD1).

Conclusion GD is prevalent among individuals in treatment for MUD in China. Network analysis suggests that gambling preoccupation and MA tolerance represent central features, and that MA tolerance serves as a bridge across GD and MUD.

Keywords Addictive behaviors, Gambling disorder, Methamphetamine use disorder, Major depressive episode, Antisocial personality disorder, Network analysis

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Introduction

Gambling disorder (GD) frequently co-occurs with substance use disorders (SUDs) [1]. These addictive behaviors share similarities in etiology, clinical features, and neurobiological substrates [2, 3]. A recent meta-analysis suggests that substance-related problems increase the likelihood of experiencing problem gambling nearly fivefold [4]. Epidemiological findings indicate that approximately 60% of people with gambling problems experience SUDs [1].

While many studies have documented associations between SUDs and GD, few have investigated relationships at the level of individual symptoms (or DSM criteria). Some previous studies have applied diagnostic criterion counts to represent the overall severity of SUDs or GD, e.g., counting the number of diagnostic criteria satisfied for SUDs and interpreting it as a severity index. However, a severity index may not consider potential differences and relationships among individual symptoms [5, 6]. Understanding the granular relationships between GD and SUDs may not only help identify common underlying factors but also promote integrated treatment approaches. For example, GD may serve as a coping mechanism, and specific SUDs (like those involving alcohol or methamphetamine (MA)) may relate to GD in specific ways. Insight into these relationships may promote the development of more effective interventions and prevention strategies.

Network analysis is a promising tool for dissecting psychopathology at the symptom level [7]. It conceptualizes mental health problems as emerging from dynamic correlations between individual symptoms. Unlike traditional approaches that rely on latent variables, network analysis examines how symptoms reinforce or inhibit one another, offering a more direct exploration of their interrelationships. By applying network analysis, we can investigate the relative contribution of symptoms within a network, identifying those that are highly influential and central [7–9]. This approach facilitates modeling symptoms from multiple constructs within a single network, enhancing understanding of their interrelationships, which can provide insights into specific features linking disorders. By definition, bridge symptoms connect distinct clusters of symptoms corresponding to different mental disorders or subgroups of symptoms within the same mental disorder [10]. Bridge symptoms may increase the likelihood of one disorder activating another [11]. Central and bridge symptoms may play vital roles in maintaining disorders and should thus receive higher priority for treatment.

Network analysis has been implemented to study the symptoms' network structures for commonly co-occurring disorders such as depression and anxiety [12, 13], and posttraumatic stress disorder and depression [14, 15]. Central and bridge symptoms may play key roles in triggering and maintaining comorbidity and are promising targets for potential clinical interventions. Several studies have evaluated the network structure of substance use disorders, including alcohol use disorder, cannabis use disorder, and cocaine use disorder [16–18], as well as addictive behaviors such as internet gaming disorder [19]. Additionally, research has explored the co-occurrences of these disorders with features of other disorders, such as GD and schizophrenia [20–22]. However, to our knowledge, no prior studies have investigated the co-occurrence of GD and SUDs through network analysis.

MA is the most prevalent illegal drug in China [23], and MA use disorder (MUD) may precipitate the next global substance use crisis [24]. A recent study suggests that the severity of GD is positively associated with MA-induced psychosis in MUD patients [25], highlighting the need to screen for and intervene in GD in treating MUD patients, particularly those with MA-induced psychosis. Currently there are very few studies exploring the co-occurrence of GD and MUD, especially at granular levels. We identified three studies that have assessed the prevalence of GD in MUD patients [25–27]. Research indicated that reducing the severity of GD may lead to a decrease in the severity of other addictive behaviors [28]. Therefore, screening for potential risk factors linking GD and MUD is particularly important, as it may aid in identifying high-risk individuals and informing integrated treatment strategies. Evaluating the prevalence, risk factors, and network structure of GD in MUD patients is important to help inform clinicians, researchers, and policymakers concerned with MUD and GD. In this study, we assessed GD among a cohort of MUD patients in drug rehabilitation centers in China. We had two main objectives: first, to explore the prevalence of and identify possible risk factors for GD among MUD patients; and second, to build a symptom network of GD and MUD and identify central and bridge symptoms within this network.

Methods

This study followed reporting standards for psychological network analyses in cross-sectional data [29].

Study setting and participants

We conducted this multicenter cross-sectional study by recruiting from five compulsory drug rehabilitation centers in China located in Changsha, Wuhan, Ningbo, Xinxiang, and Chengdu. Individuals found to have used any kinds of amphetamine, morphine, ketamine, and marijuana in the last six months through a hair drug test were sent to the rehabilitation facilities for detoxification management. Recruitment started in December 2017

and ended in December 2019. Individuals who were diagnosed with MUD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) were eligible for the study [30, 31]. We excluded participants diagnosed with schizophrenia.

All participants voluntarily chose to participate in the study, free from coercion. Before participation, all individuals were thoroughly informed about the study's aims, procedures, and potential benefits and risks involved. They were also explicitly told that they could withdraw from the study at any time without any consequences. Informed consent was obtained from each participant before the study commenced. The study was reviewed and approved by the Second Xiangya Hospital of Central South University (No.2017064).

Participant assessment

All participants were interviewed face-to-face by a trained interviewer and assessed using the Semi-Structured Assessment for Drug Dependence and Alcoholism (SSADDA) Chinese version, a validated instrument with excellent psychometric measures for substance use and psychiatric disorders [32, 33]. The SSADDA is a comprehensive instrument that collects demographic characteristics such as age, sex, education level, marital status, and employment status and other information described below. Details concerning the development of the Chinese SSADDA and information about the interviewers are available in the supplementary materials.

Characteristics of methamphetamine use

We documented the age at initial MA use, duration of MA use, MA-related periods of abstinence, polysubstance use, and treatment history.

Other substance use and gambling

The SSADDA assessed lifetime use of other substances, including alcohol, tobacco/nicotine, ketamine, opioid, cannabis, stimulants, and sedatives. Lifetime substance use was defined as use on more than ten occasions, based on the SSADDA threshold to distinguish habitual use from occasional or experimental use. Diagnoses of GD, alcohol use disorder, ketamine use disorder, and opioid use disorder were established based on DSM-5 criteria, while nicotine dependence was diagnosed according to DSM-IV diagnostic criteria because the SSADDA did not elicit the craving information needed for DSM-5 diagnosis. Gambling duration was assessed.

Other psychiatric disorders or concerns

The SSADDA assessed MA-related psychosis, including delusions, hallucinations, suspiciousness, difficulty concentrating, nervousness, social withdrawal, panic, mania, fear, and irritability. Detailed descriptions of these psychological variables are provided in the supplementary materials. The SSADDA also assessed for major depressive episodes (MDEs) and antisocial personality disorder (ASPD) based on DSM-5 diagnostic criteria.

Suicidality and self-harm

Information was collected regarding suicidal ideation, plans, attempts, and non-suicidal self-harm.

Childhood experiences

The SSADDA also collected information regarding childhood attention deficit hyperactivity disorder (ADHD) symptoms and childhood experiences, including witnessing or experiencing violence, death of parents, family history of substance use, and number of residential moves.

Analytical approaches

Descriptive analyses

All descriptive analyses were conducted using R (version 4.1.1) [34]. For continuous variables, we report median and interquartile range (IQR; 25–75%), and for categorical variables, frequencies and percentages.

Univariate and multivariate analyses

Chi-square and Wilcoxon rank-sum tests compared GD and non-GD groups in the cohort of individuals with MUD. Bonferroni corrections were employed to adjust for multiple testing (corrected $p = 0.05/49 = 0.001$). The multivariate logistic regression model, using the enter method (including all independent variables in the model simultaneously), included variables that were statistically significant in the univariate analyses, along with age and sex. All tests were two-tailed, with $p < 0.05$ designating statistical significance.

Network analysis

Symptoms of GD and MUD were recorded as 0 (absent) and 1 (present) according to diagnostic criteria. Table 1 presents the symptom items of GD and MUD. We used the function described in the R package *psych* to evaluate the mean and standard deviation (SD) of each diagnostic criterion of GD and MUD. The R function *goldbricker* in the *networktool* package was used to identify redundant symptoms (with similar underlying content) [35].

We visualized and estimated the networks using the R packages *qgraph* and *bootnet* [7, 36]. When network items were binary, we used the *Ising* model implemented in the R package *IsingFit* to estimate the network [29]. In network models, each symptom was considered a node. To determine and screen network edges between two symptoms, we used the logistic regression coefficients after controlling for covariates in the network. Following

Table 1 Characteristics of MUD and GD symptoms

Items	Labels	Criteria	Presence (%)	EI
MUD1	Time spent using	A great deal of time is spent in activities necessary to obtain, use, or recover from the effects of methamphetamine	46	0.45
MUD2	Health	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by methamphetamine	54	0.48
MUD3	Quit	There is a persistent desire or unsuccessful attempts to cut down or control methamphetamine use	76	− 1.15
MUD4	Intention to use MA	Methamphetamine is taken in larger amounts or over a longer period than intended	34	0.34
MUD5	MA tolerance	1. A need for markedly increased amounts of methamphetamine to achieve intoxication or desired effect 2. Markedly diminished effect with continued use of the same amount of methamphetamine	29	0.62
MUD6	Giving up important activities	Important social, occupational, or recreational activities are given up or reduced because of methamphetamine use	53	0.64
MUD7	Withdrawal	1. Characteristic withdrawal syndrome for methamphetamine 2. Methamphetamine (or a closely related substance) is taken to relieve or avoid withdrawal symptoms	76	− 0.53
MUD8	Craving	Craving, or a strong desire or urge to use the stimulant	50	− 0.27
MUD9	Neglected	Recurrent methamphetamine use results in a failure to fulfill major role obligations at work, school, or home	52	− 1.07
MUD10	Social	Continued methamphetamine use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the drug	86	− 1.43
MUD11	Hazard	Recurrent methamphetamine use in situations in which it is physically hazardous (e.g., driving under the influence)	44	− 1.69
GD1	Preoccupation	Frequent thoughts about gambling (e.g., reliving past gambling experiences, planning the next venture, or thinking of ways to obtain money to gamble)	63	2.74
GD2	Increasing money	Requires more money to achieve the desired level of excitement, indicating tolerance	35	0.20
GD3	Unsuccessful quit	Repeated attempts to reduce or quit gambling have been unsuccessful	27	− 0.05
GD4	Withdrawal	Experiences withdrawal symptoms when trying to reduce or stop gambling	19	− 0.54
GD5	Relief	Uses gambling as a way to cope with feelings of helplessness, guilt, anxiety, or depression	21	− 0.92
GD6	Chasing losses	Chasing losses: After losing money, returns on another day to get even ("chasing" one's losses)	54	0.60
GD7	Lie	Deceives family members, therapists, or others about the degree of involvement in gambling	37	0.35
GD8	Lost opportunities	Because of gambling behavior, there is a significant loss or risk of losing these important aspects of life	36	0.61
GD9	Financial trouble	Requires financial help from family, friends, or others to relieve desperate financial situations caused by gambling	52	0.63

MA: methamphetamine; MUD: methamphetamine use disorder; GD: gambling disorder; EI: expected influence

established guidelines [37], an edge between two nodes was defined by a logistic regression coefficient of ≥ 0.25, as implemented in the R package, IsingFit. This cutoff minimizes the risk of false positives while preserving the most significant associations. A red edge represented a negative association, while a blue edge showed a positive association. The thickness of the edges indicated the strength of association between symptoms, with thicker edges indicating stronger associations [38].

The centrality index expected influence (EI) was used in the R package *qgraph* to demonstrate the importance of a symptom in the network [11]. It was calculated by summing the weights of the edges connecting a node to other nodes directly, with positive edges allowed to offset negative edges. A node with the highest EI is considered a hub, or central symptom, which substantially impacts other nodes. Bridge expected influence (BEI) was used to identify the bridge symptoms linking GD and MUD. BEI was defined similarly to EI by summing a node's edge weights that connect nodes from GD to those from MUD [39] (i.e., edges linking symptoms within GD or MUD do not count in BEI). Based on prior research, an empirical cutoff at the 80th percentile of the BEI threshold was used to identify bridge symptoms [40, 41].

We employed a nonparametric bootstrapping procedure via the R package *bootnet* to test the accuracy of the predicted edge using 1000 bootstrap samples. We also used a case-dropping bootstrap approach to assess the stability of the center's expected influence [38]. The correlation stability coefficient represents the stability of the network. A correlation stability coefficient higher than 0.25 was considered acceptable.

Results

Sample characteristics and univariate analysis

We interviewed 1069 patients, of whom 711 met the inclusion criteria (Table 2). More than half of MUD patients (371, 52.3%) also met DSM-5 diagnostic criteria for GD. Most participants were male (635, 89%). The median age was 32 [28, 37] years, and the median duration of daily MA use was 2 [12] months. Based on the DSM-5 MUD severity definition, 191 (27%) individuals had mild MUD, 111 (16%) had moderate MUD, and 409 (58%) had severe MUD.

After Bonferroni correction, we observed no difference in the demographic information (age, sex, employment status, and married status) between participants with and without GD ($p > 0.001$). Participants with GD met more DSM-5 criteria for MUD and had a higher likelihood of DSM-5 severe MUD (73% vs. 41%, $p < 0.001$). MA patients with polysubstance use, such as alcohol or other drug use, were more prone to GD ($p < 0.001$). However, the two groups had no difference in other MA-use-related variables (adjusted $p > 0.05$). As for the psychotic symptoms, MUD participants with GD versus those without GD were more likely to have experienced MA-induced loss of concentration (29% vs. 19%, $p < 0.001$), MA-induced social withdrawal (77% vs. 57%, $p < 0.001$), self-harm (8.4% vs. 2.6%, $p < 0.001$). There was a higher prevalence of lifetime MDE (16% vs. 5.9%, $p < 0.001$) and ASPD (40% vs. 21%, $p < 0.001$) among MUD participants with GD vs. those without GD. There was no difference between MUD with GD vs. MUD without GD in the likelihoods of MA-induced hallucinations and delusions, suspiciousness, and nervousness. Moreover, irritability, compulsive thoughts, fear, anxiety symptoms, suicidal thoughts, and suicide attempts did not differ among MUD participants with GD vs. those without GD.

MUD participants with GD vs. those without GD were more likely to have lifetime ketamine use (16% vs. 7.1%, $p < 0.001$) and ketamine use disorder (14% vs. 5.9%, $p < 0.001$). A similar pattern was observed for cannabis use (3.5% vs. 1.2%, $p = 0.005$), although the difference was not significant after Bonferroni correction. No between-group differences were observed for other SUDs and substance lifetime experience.

Regarding traumatic childhood experiences, MUD participants with GD vs. those without GD were more likely to have experienced violence before age 13 years (9.7% vs. 2.6%, $p < 0.001$). No relationship between GD and childhood ADHD symptoms, death of parents before age 6, and substance use among family members was observed.

Multivariate analyses

The following variables were incorporated into the multivariate analysis: sex, age, age of first MA use, concurrent substance use, severe MUD, MA-loss of concentration, MA-social withdrawal, self-harm, suicide attempt, MDE, ASPD, ketamine lifetime use, ketamine use disorder, childhood exposure to violence, and gambling duration. In the final model (Table 3), the following factors were independently associated with GD among MUD participants: female sex (odds ratio (OR) = 0.52; 95% confidence interval (CI) 0.27–0.99; p = 0.046), concurrent alcohol use with MA (OR = 1.97; 95% CI 1.28–3.03; p = 0.002), childhood violence experiences (OR = 2.83; 95% CI 1.17–6.87; p = 0.021), MDEs (OR = 2.31; 95% CI 1.27–4.23; p = 0.006), severe MUD (OR = 2.53; 95% CI 1.68–3.80; p < 0.001), and gambling duration (OR = 1.15; 95% CI 1.11–1.18; p < 0.001).

Network analysis

No items in the MUD and GD criteria were excluded for low informativeness or redundancy. Figure 1 illustrates the network of GD and MUD symptoms. Table 1 displays the details of each MUD and GD symptoms. The network density (i.e., the portion of actual connections among all the possible connections in a network) was 0.363 (69/190 edges). The strongest edges within the network were between 'intention to use MA' (MUD4) and 'MA tolerance' (MUD5), followed by 'chasing losses' (GD6) and 'financial trouble' (GD9). According to the bootstrapping procedure, 'gambling preoccupation' (GD1) was identified as the most central symptom, which exhibited a statistically higher centrality index EI than other nodes within the network (Figure S1). Other central symptoms included 'giving up important activities' (MUD6), 'financial trouble' (GD9), and 'MA tolerance' (MUD5) (Fig. 2a). These features may play important roles in triggering and maintaining the GD-MUD network. MA tolerance (MUD5) and hazard (MUD11) were bridge symptoms; they linked the GD and MUD networks and may drive co-occurrence (Fig. 2b). 'MA tolerance' (MUD5) was positively associated with 'gambling preoccupation' (GD1), while 'hazard' (MUD11) was positively associated with gambling with 'increasing amounts of money' (GD2) and 'withdrawal' (GD4).

The network had good stability, with a correlation stability coefficient of node expected influence at 0.672. This

Table 2 Basic information and clinical characteristics of MUD patients

Variables	Overall, N = 711	Without GD, N = 340	With GD, N = 371	χ^2/Z	p-value
Basic information					
Sex				8.02	0.005
Male	635 (89%)	292 (86%)	343 (92%)		
Female	76 (11%)	48 (14%)	28 (7.5%)		
Age, years*	32 (28, 37)	33 (29, 39)	31 (28, 36)	− 2.61	0.009
Employment status (Yes)	320 (45%)	145 (43%)	175 (47%)	1.47	0.2
Marital Status				1.05	0.3
Married	263 (37%)	119 (35%)	144 (39%)		
Single or divorced	447 (63%)	220 (65%)	227 (61%)		
MA-related information					
MA first use age, years*	25 (20, 31)	25 (21, 32)	24 (20, 29)	− 3.21	**0.001**
Substance used to avoid or relieve withdrawal				6.21	0.026
None	549 (77%)	276 (81%)	273 (74%)		
Alcohol	152 (21%)	62 (18%)	90 (24%)		
Other drugs	10 (1.4%)	2 (0.6%)	8 (2.2%)		
Concurrent substance use				**16.43**	**< 0.001**
None	488 (69%)	259 (76%)	229 (62%)		
Alcohol	164 (23%)	58 (17%)	106 (29%)		
Other drugs	59 (8.3%)	23 (6.8%)	36 (9.7%)		
Withdrawal symptoms	512 (72%)	234 (70%)	278 (76%)	3.09	0.089
Abstinent for at least 3 months	509 (72%)	245 (72%)	264 (71%)	0.07	0.8
Consult with doctors	33 (4.6%)	17 (5.0%)	16 (4.3%)	0.19	0.7
Receive Treatment	41 (5.8%)	22 (6.5%)	19 (5.1%)	0.59	0.4
Severe MUD	409 (58%)	140 (41%)	269 (73%)	**71.27**	**< 0.001**
Psychological symptoms					
MA-delusion	212 (30%)	93 (27%)	119 (32%)	1.89	0.2
MA-loss of concentration	172 (24%)	63 (19%)	109 (29%)	**11.39**	**< 0.001**
MA-suspiciousness	160 (23%)	66 (19%)	94 (25%)	3.57	0.059
MA- hallucination	97 (14%)	47 (14%)	50 (13%)	0.02	0.9
MA- nervousness	178 (25%)	79 (23%)	99 (27%)	1.12	0.3
MA-social withdrawal	478 (67%)	193 (57%)	285 (77%)	**32.39**	**< 0.001**
Self-harm	40 (5.6%)	9 (2.6%)	31 (8.4%)	**10.89**	**< 0.001**
Suicidal thoughts	66 (9.3%)	26 (7.6%)	40 (11%)	2.07	0.2
Suicidal plan	28 (3.9%)	11 (3.2%)	17 (4.6%)	0.85	0.4
Suicidal attempt	21 (3.0%)	5 (1.5%)	16 (4.3%)	5.00	0.025
Auditory hallucinations	85 (12%)	35 (10%)	50 (13%)	1.71	0.2
Anxiety	18 (2.5%)	11 (3.2%)	7 (1.9%)	1.31	0.3
Compulsive thoughts	12 (1.7%)	8 (2.4%)	4 (1.1%)	1.74	0.2
Feeling afraid	30 (4.2%)	11 (3.2%)	19 (5.1%)	1.56	0.2
Panic	15 (2.1%)	12 (3.5%)	3 (0.8%)	6.36	0.012
Manic Episode	108 (15%)	40 (12%)	68 (18%)	5.93	0.015
Irritability	81 (11%)	36 (11%)	45 (12%)	0.42	0.5
MDE	80 (11%)	20 (5.9%)	60 (16%)	**18.81**	**< 0.001**
ASPD	210 (30%)	87 (21%)	123 (40%)	**25.07**	**< 0.001**
Other substance use experience					
Cannabis lifetime use	17 (2.4%)	4 (1.2%)	13 (3.5%)	4.12	0.042
Simulant lifetime use	13 (1.8%)	7 (2.1%)	6 (1.6%)	0.19	0.7
Sedative lifetime use	3 (0.4%)	1 (0.3%)	2 (0.5%)	0.25	> 0.9
Ketamine lifetime use	85 (12%)	24 (7.1%)	61 (16%)	**14.84**	**< 0.001**

Table 2 (continued)

Variables	Overall, N = 711	Without GD, N = 340	With GD, N = 371	χ^2/Z	p-value
Opioid lifetime use	25 (3.5%)	14 (4.1%)	11 (3.0%)	0.69	0.4
Tobacco lifetime use	685 (96%)	325 (96%)	360 (97%)	1.05	0.3
Alcohol lifetime use	617 (87%)	295 (87%)	322 (87%)	0	> 0.9
Other substance use disorder					
Ketamine use disorder	72 (10%)	20 (5.9%)	52 (14%)	**12.90**	**< 0.001**
Alcohol use disorder	194 (27%)	91 (27%)	103 (28%)	0.09	0.8
Opioid use disorder	22 (3.1%)	11 (3.2%)	11 (3.0%)	0.04	0.8
Nicotine dependence	171 (24%)	74 (22%)	97 (26%)	1.86	0.2
Childhood experience					
Death of parents before age 6	40 (5.6%)	14 (4.1%)	26 (7.0%)	2.79	0.095
Experienced violence before age 13	45 (6.3%)	9 (2.6%)	36 (9.7%)	**14.90**	**< 0.001**
Experienced sexual abuse before age 13	1 (0.1%)	1 (0.3%)	0 (0%)	1.09	0.5
Family member substance use	290 (41%)	132 (39%)	158 (43%)	1.04	0.3
Ever in daycare before kindergarten	55 (7.7%)	32 (9.4%)	23 (6.2%)	2.57	0.11
ADHD symptoms	58 (8.2%)	23 (6.8%)	35 (9.4%)	1.69	0.2
*Gambling duration (years)**	2 (0, 12)	0 (0, 1)	6 (3, 12)	**18.70**	**< 0.001**

Bold suggested statistical significance

GD, Gambling disorder; MA, methamphetamine; MUD, methamphetamine use disorder; MDE, major depressive episodes; ASPD, antisocial personality disorder; ADHD, attention deficit hyperactivity disorder

* Data descriptive with median (interquartile range)

Table 3 Factors associated with GD in patients with MUD: the univariate and multivariate logistic regression analysis

Variables	*P*	COR (95%CI)	*P*	AOR (95%CI)
Sex	**0.005**		**0.046**	
Male		1.00 (Reference)		1.00 (Reference)
Female		0.50 (0.30 ~ 0.81)		**0.52 (0.27 ~ 0.99)**
Age	**0.008**	0.97 (0.95 ~ 0.99)	0.439	0.99 (0.96 ~ 1.02)
Gambling duration	**< 0.001**	1.17 (1.13 ~ 1.20)	**< 0.001**	1.15 (1.11 ~ 1.18)
Concurrent substance use	**< 0.001**		**0.002**	
None		1.00 (Reference)		1.00 (Reference)
Alcohol		2.07 (1.43 ~ 2.98)		**1.97 (1.28 ~ 3.03)**
Other drugs	**0.043**	1.77 (1.02 ~ 3.08)	0.366	1.37 (0.69 ~ 2.72)
Ketamine lifetime usage	**< 0.001**	2.59 (1.58 ~ 4.26)	0.154	2.03 (0.77 ~ 5.36)
Childhood violence experience	**< 0.001**	3.95 (1.87 ~ 8.33)	**0.021**	2.83 (1.17 ~ 6.87)
MA-loss of concentration	**< .001**	1.83 (1.28 ~ 2.60)	0.379	1.22 (0.78 ~ 1.90)
MA-social withdrawal	**< 0.001**	2.52 (1.83 ~ 3.49)	0.198	1.32 (0.86 ~ 2.03)
Self-harm	**0.002**	3.35 (1.57 ~ 7.15)	0.096	2.16 (0.87 ~ 5.36)
APSD	**< 0.001**	2.34 (1.67 ~ 3.27)	0.387	1.21 (0.79 ~ 1.85)
Ketamine use disorder	**< 0.001**	2.61 (1.52 ~ 4.47)	0.826	0.89 (0.31 ~ 2.56)
MDE	**< 0.001**	3.09 (1.82 ~ 5.24)	**0.006**	**2.31 (1.27 ~ 4.23)**
Severe MUD	**< 0.001**	3.77 (2.75 ~ 5.16)	**< 0.001**	**2.53 (1.68 ~ 3.80)**

Bold suggested statistical significance

COR, crude odds ratio; AOR, adjusted odds ratio; GD, Gambling disorder; MA, methamphetamine; MUD, methamphetamine use disorder; MDE, major depressive episodes; APSD, antisocial personality disorder

indicates that 67.2% of the raw data could be omitted, while the network maintained a correlation of 0.7 for the original data with 95% certainty (Figure S2). Results of the nonparametric bootstrapping suggested that the 95% CIs were rather broad (Figure S3). The order of edge estimates should, therefore, be interpreted with caution.

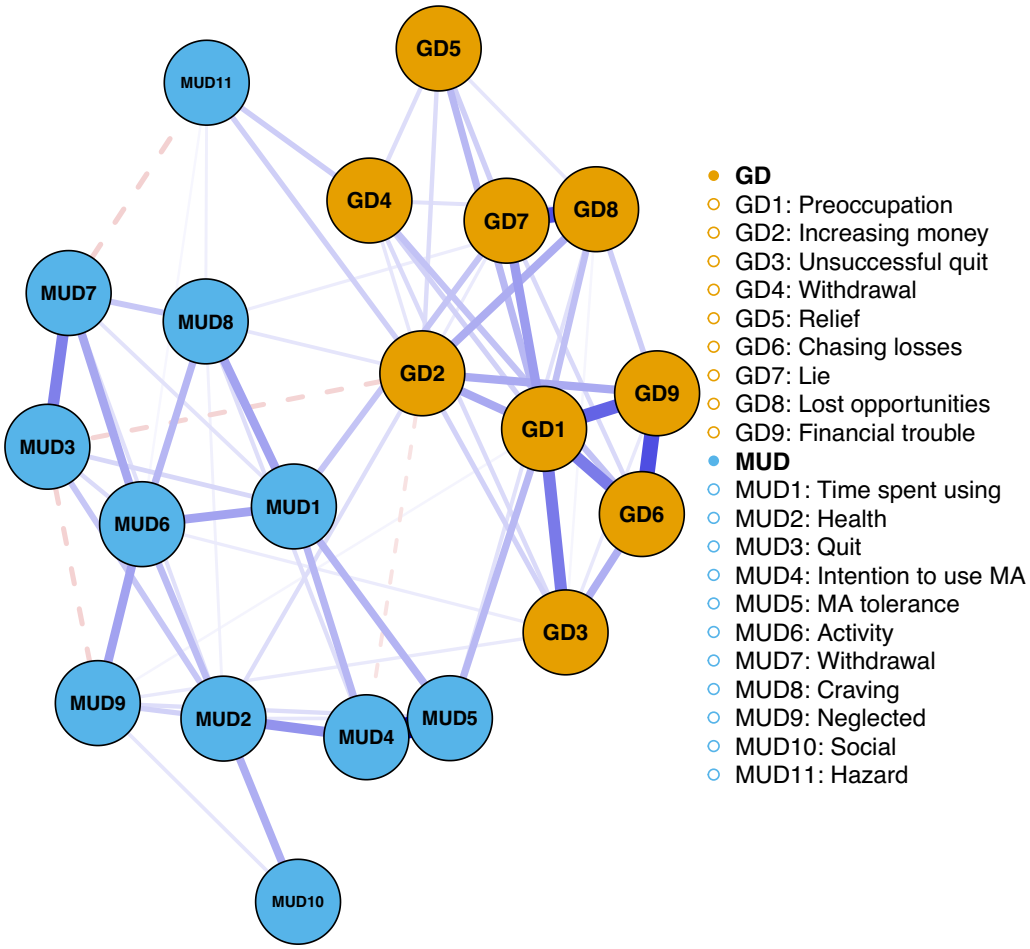

Fig. 1 The symptom network of MUD-GD. Orange nodes represent GD features, and blue nodes represent MUD features. The blue edges indicate positive associations and red edges indicate negative associations between two symptoms. The thickness of the edges represents the strength of the association between two nodes, with greater thickness indicating stronger relationship

Discussion

To the best of our knowledge, this is the first study to document concurrently the prevalence, correlates, and network structure of GD among individuals with MUD. We found that 52% of MUD participants also met DSM-5 criteria for GD. Independent potential risk factors for GD include being male, combined alcohol use with MA use, childhood violent experiences, MDEs, severe MUD, and gambling duration. In the GD-MUD network, the most central symptoms were 'gambling preoccupation' (GD1) and 'giving up important activities' (MUD6), followed by 'financial trouble' (GD 10) and 'MA tolerance' (MUD5). 'MA tolerance' (MUD5) also served as a bridge symptom between GD and MUD symptoms among MUD patients. Our work identifies a potential target for symptomatological screening and intervention for GD in MUD patients.

To date, few studies have focused on GD in MUD. In our study, more than half of the MUD patients met diagnostic criteria for GD. The prevalence of GD in MUD patients was higher than in previous studies among the general Chinese population (~1.8–1.9%) [42, 43], suggesting that MUD might increase the risk of GD or vice versa. Studies in different cultural groups have shown similar results. For example, a longitudinal study of alcohol, substance use, and gambling behaviors recruited college students (N = 4,640) at multiple academic campuses in California, Texas, and Florida in the US found that using amphetamine-type stimulants at baseline statistically predicted the presence of GD [44]. Another study among high-school students (N = 6542) in the US suggested an 8.3-fold increase in likelihood for gambling problems in people using (versus not using) MA [45]. Compared with similar studies in Chinese MUD patients (5% to 45%) [25–27], we found that the prevalence of GD in the present study was also higher than in previous reports. The popularity of MA and the increased access to gambling in recent years may have contributed to this apparent increase in co-occurring GD and MUD [23, 46].

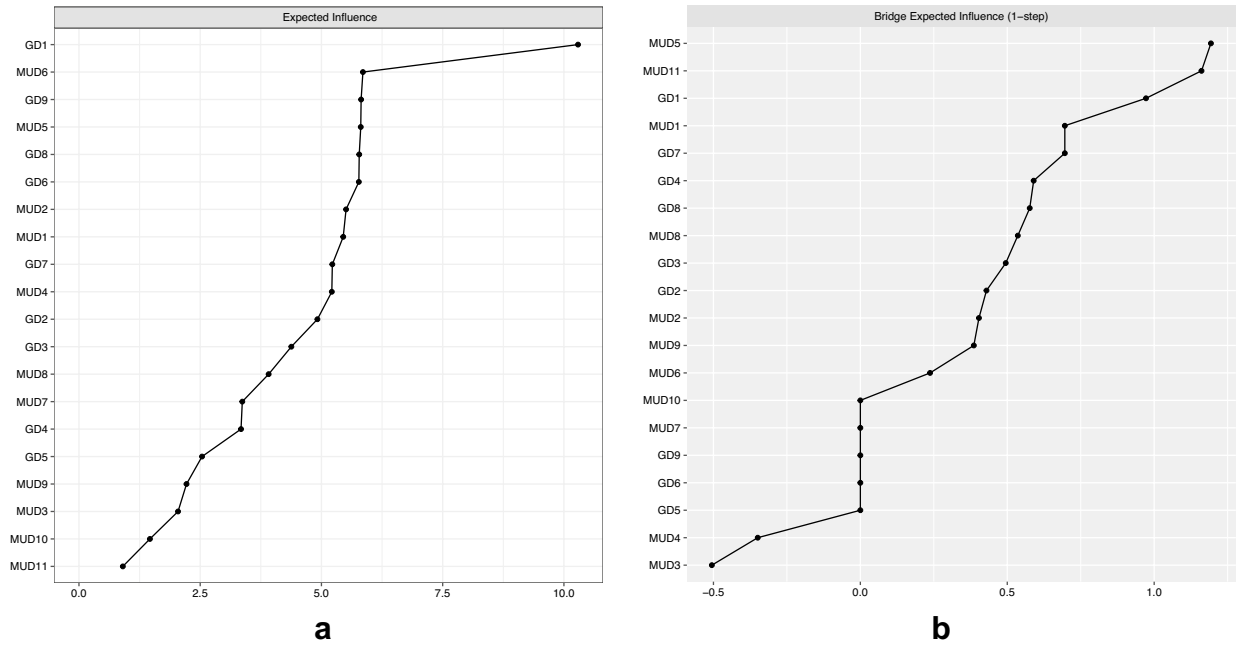

Fig. 2 The central and bridge symptom of the MUD-GD network. **a** The node expected influence plot. The X-rays represent the expected influence of each node. Nodes with higher expected influence have stronger impact on other nodes within the network. **b** The bridge expected influence plot. The X-rays represent the bridge-expected influence of each node. Nodes with higher bridge-expected influence are recognized as bridge symptoms that may drive the co-occurrence of MUD and GD

Our study suggests that GD may be closely linked to MA-related characteristics. GD patients had longer MA use duration and more severe MUD, which was in line with the finding by Krmpotich et al. [47]. Speculatively, similarities in neurobiological substrates of GD and MUD may contribute to associations [48–50], including with respect to dysregulation in the ventral medial prefrontal cortex and ventral striatum [51–53]. Despite the frequent co-occurrence of GD and SUDs, relatively few studies have investigated interventions to treat this co-occurrence. The co-occurrence may result in poor treatment outcomes [54]; thus, more research is needed to develop appropriate interventions and treatments.

In addition to MA-related characteristics, using other substances (i.e., ketamine and alcohol) also were associated with GD. Individuals with polysubstance use may represent a susceptible population, considering that they exhibit longer MA use, have more physical and psychiatric comorbidities, and have more significant cognitive deficits [55–57]. Overlapping vulnerability factors among SUDs and GD may contribute to the co-occurrence of GD and MUD [58].

Our study identified childhood experience of violence as a significant factor linking MUD-GD co-occurrence. Previous research has also associated childhood trauma with both MUD and GD [59, 60]. Individuals who have experienced childhood violence may turn to gambling as a coping strategy to manage emotional distress stemming from such adverse experiences [61, 62]. Moreover, childhood violence experience may alter the brain's reward system, increasing susceptibility to addictive behaviors like gambling, which may activate these pathways and provide temporary relief from the negative emotions associated with childhood violence experiences [63]. We also found that MDEs were independently linked to GD, here in the context of MUD, in line with previous epidemiological studies in the general population [64, 65]. Self-harm and suicidal attempts also were linked to GD among MUD patients. A bidirectional relationship between MDEs and GD has been suggested [66, 67]. One possible explanation for links between MDEs and GD may reflect self-medication or maladaptive coping strategies [68, 69]. People may gamble as a maladaptive coping mechanism to relieve or escape negative emotions and have difficulties controlling their gambling behaviors. As the co-occurrence between major depressive disorder and GD in a large cohort of male twins has been found to reflect predominantly shared genetic underpinnings [70], specific genetic factors also warrant strong consideration.

Network analysis illustrates symptom-symptom correlations between MUD and GD. Among the most central nodes of the GD-MUD network were gambling preoccupation (GD1) and MA tolerance (MUD5). The high centrality of gambling preoccupation replicated findings

from Mestre-Bach et al., which reported that preoccupation could be the most central symptom of GD in 739 treatment-seeking patients [21]. Preoccupation was also identified as the core symptom in previous network analyses of other behavioral addictions, such as internet gaming disorder and internet addiction [71, 72]. Preoccupation may serve as a common core characteristic among different addictive behaviors. Our finding is also in accordance with Temcheff and colleagues' findings that preoccupation, among all DSM-5 diagnostic criteria for GD, was particularly salient for identifying people with gambling problems [73]. Being preoccupied with gambling has been linked to poor impulse control [74] and poor self-regulation [75]. Cognitive factors have also been associated with behavioral addictions; individuals with GD may have diminished cognitive resources to control their behaviors. As with SUDs, people with GD may feel pleasure when gambling but may feel distressed when stopping or encountering losses [76]. These factors may relate to preoccupation, and future studies should directly examine these possibilities.

MA tolerance (MUD5) also served as a bridge symptom between GD and MUD. We speculate that MUD and GD have similar vulnerability mechanisms. Dopaminergic reward systems may explain both MUD and GD [77], although this possibility has not been consistently supported. Arguably more consistent results have been observed across GD and SUDs for a reward deficiency hypothesis. Blunted striatal activation to non-addiction rewards, especially during an anticipatory phase, has been observed across SUDs and GD [78]. Furthermore, treatment of SUDs has been linked to increased striatal activation during the same phase of reward processing, suggesting "improvement" or "normalization" with treatment [79, 80]. Such blunted striatal processes may relate to tolerance [81]. When tolerance increases a reward threshold, an individual may experience motivations to engage in addictive behaviors like gambling or MA use, and this currently speculative notion warrants direct investigation in the future.

The present study has several clinical implications. First, we found that more than 50% of MUD patients in drug rehabilitation centers experienced GD, which was associated with severe MUD. This finding suggests a need for screening, identification and treatment of GD in this population. Early detection and treatment of GD among MUD patients may help improve treatment outcomes. Second, our study linked multiple factors to GD in MUD patients, which enriches our understanding of potential risk factors for GD and may help in the early detection of GD. Third, network analysis provided new insights into relationships between GD and MUD. Targeting central and bridge symptoms, i.e., GD-related preoccupation and MA tolerance, may be clinically valuable in preventing and treating GD in MUD patients.

In summary, we recruited 1069 participants, of whom 711 met DSM-5 criteria for MUD. GD was highly prevalent among MUD patients. Network analysis suggested that preoccupation was a central symptom of GD and that MA tolerance was a bridge symptom between the two disorders.

The cross-sectional design limits causal implications, as we did not ascertain the chronological order in which GD and MUD occurred. Moreover, participants were recruited from drug rehabilitation centers, and most were male. Thus, findings may not represent relationships between GD and MUD in females or in the general population in China or other jurisdictions. It remains unknown whether findings generalize to other populations. Further studies in community samples with longitudinal designs are needed. Another limitation of this study is that the broad 95% CIs from the nonparametric bootstrapping suggest that the edge estimates may not be entirely reliable, which restricts direct comparisons of edge strength. Thus, caution is required when interpreting these results, and further studies with larger sample sizes are needed to validate these findings. Finally, while this study provides insights into the granular relationships between MUD and GD, further research is needed to determine whether these findings generalize to other SUDs, such as alcohol or opioid use disorders. The interaction patterns may differ depending on the specific effects of each substance or behavior, which could have implications for tailored treatment approaches.

Supplementary Information

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Supplementary material 1.

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Author contributions
Tieqiao Liu was responsible for study design, manuscript preparation, revision, and supervision. Bao-Zhu Yang worked closely with the co-first authors to guide the analyses, interpret the results, and comment on and revise the manuscript. Pu Peng and Yuzhu Hao also contributed to developing the study design, undertook the statistical analysis, and wrote the first draft of the manuscript. Xiaojie Zhang, Yuejiao Ma, Xuebing Liu, Danlin Shen, Wenwen Shen, Bin Zhao, Ruiling Zhang, and Dongxiao Li were all involved in sample recruitment and manuscript editing. Yaira Z. Nunez, Sarah E. Beck, Marc N. Potenza and Joel Gelernter reviewed and edited the manuscript. Bao-Zhu Yang, Yaira Z. Nunez, and Joel Gelernter also contributed to the SSADDA translation into the Chinese version. All authors read and approved the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
All participants gave written informed consent before participating in the study. The ethics committee of the Second Xiangya Hospital of Central South University approved this study (No.2017064).

Competing interests
MNP has consulted for Baria-Tek and Boerhinger Ingelheim; has been involved in a patent application with Yale University and Novartis; has received research support from the Mohegan Sun Casino and the Connecticut Council on Problem Gambling; has participated in surveys, mailings or telephone consultations related to drug addiction, impulse-control disorders or other health topics; has consulted for and/or advised gambling, non-profit, healthcare and legal entities on issues related to impulse-control, internet use and/or addictive disorders; has performed grant reviews for research-funding agencies; has edited journals and journal sections; has given academic lectures in grand rounds, CME events and other clinical or scientific venues; and has generated books or book chapters for publishers of mental health texts. Dr. Gelernter is named as an inventor on PCT patent application #15/878,640 entitled: "Genotype-guided dosing of opioid agonists," filed January 24, 2018 and issued on January 26, 2021 as U.S. Patent No. 10,900,082. Dr. Gelernter is paid for editorial work for the journal "Complex Psychiatry." The other authors report no disclosures.

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